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Histidine Metabolism in Normal and Toxaemic Pregnancy. The Excretion of Histidine in Normal Pregnancy Urine and in the Urine of Patients with Toxaemia of Pregnancy *

BY

R. KAPELLER-ADLER, Ph.D., Vienna

From the Institute of Animal Genetics and from the Biochemical Laboratory of the Royal Infirmary, Edinburgh.

IN 1934 the writer described a simple reaction for demonstrating the presence of histidine in the urine, and the results obtained by investigating about 300 pregnant and non-pregnant women proved that this test may be used for the diagnosis of pregnancy.[1] By means of this method, slightly modified,[2] it was shown in 1936 that histidine is a normal constituent of the urine of women throughout the whole of pregnancy, that it appears in the urine at the very beginning of gestation and disappears from it after delivery or abortion.

Histidinuria is characteristic only of human gestation; histidine not being excreted during the pregnancy of animals.[3] Further studies revealed the existence of a relation between the excretion of histidine and that of gonadotropic hormones in pregnancy.[4]

Since then systematic investigations of several thousand specimens of urine from pregnant and non-pregnant individuals have been carried out by the author and the following results have been obtained. Evidence was found suggesting that human pregnancy does not exist without a distinct and con-

* The substance of this paper, and the subsequent one, was reported at a meeting of the Biochemical Society in Edinburgh, on June 8th, 1940.

tinuous excretion of histidine during the whole gestation period, the histidine reactions obtained ranging from a positive to a strong positive, and the quantitative figures ranging from 15 to 50 mgm. histidine per cent. The rate of histidine excretion seems to be at least partly dependent on the kind of food taken.[5]

Further it was observed that investigation of alkaline urines involves certain difficulties in testing for the presence of histidine but that these could be overcome by a preliminary treatment of such urines with N / 10 $KMnO_4$ in sulphuric acid solution. When applying this modification to the investigation of alkaline urines of pregnancy almost 100 per cent accuracy can be obtained with this test in cases of normal pregnancy, whereas in 3 per cent of non-pregnant women positive results were reported by the author.[2] It should be pointed out, however, that positive results in the urine of the non-pregnant woman were only sporadically found, whereas the pregnant woman continuously excretes histidine throughout gestation. Moreover I believe that the colour reaction sometimes obtained in non-pregnancy urine may be caused, not by the presence of histidine in those urines, but by another still unknown compound, since the colour reaction in the urine of women who are not pregnant exhibits different qualities from that given by the urine of pregnant women.

Neuweiler and Grimm[6] using the histidine test on the urine of 247 women between the 5th and 9th months of pregnancy obtained positive results in all 247 cases. In the urine of pregnant women between the 1st and 4th months they obtained negative results in 2 cases, in one of which the urine was alkaline. These authors, therefore, claim to have obtained an accuracy of 99.3 per cent. Applying this test to the investigation of non-pregnant women, Neuweiler and Grimm observed a positive colour reaction in 15 per cent of the cases. It may, however, be mentioned that among the cases investigated were those of hydatidiform mole and of abortion in which the histidine reaction is usually positive. These authors also point to the transitory character of the positive result in women not pregnant.

With regard to the date of the first appearance of histidinuria in early pregnancy, it may be stated that a positive histidine reaction may be obtained as early as the 1st week after the first missed period, and sometimes even before a period has been missed. A positive histidine test is given as well in cases of ectopic pregnancy.

Attention may be drawn to one case which the author came across quite recently. On December 7th, 1940, a histidine test was made in the urine of a woman, 27 years of age, who had had her last period on November 10th. She started bleeding on November 19th, and had continued to bleed. She had pains in the right iliac region. The histidine reaction gave a weak positive result. On December 12th the patient was operated upon, and ectopic gestation in the right Fallopian tube was found.

It may be mentioned that in early pregnancy the histidine reaction sometimes gives positive results sooner than the Aschheim-Zondek test or the Friedmann test. Neuweiler[6] and Blaufuss[7] report similar observations. Westberg[8] found a positive histidine test in 7 cases of very early pregnancy (later clinically confirmed) whereas the Aschheim-Zondek test made at the same time gave negative results. In early pregnancy the histidine test seems to be more sensitive than the biological reactions.

In cases of threatened abortion the results of the histidine reaction vary from a weak positive to a positive. In one case of threatened abortion the histidine test gave a normal positive as did the Friedmann test, whereas the Aschheim-Zondek reaction was a weak positive. In another case of threatened abortion the histidine test was positive, the Aschheim-Zondek test giving a weak positive result.

In missed abortion only a weak positive histidine test is usually obtained.

Histidine tests in cases of hydatidiform mole are always positive. Histidinuria occurs also in cases of over-function of the anterior lobe of the pituitary gland in which the Aschheim-Zondek reaction is also positive. (Norpoth[9], Kapeller-Adler and Boxer.[10])

The conditions of histidine metabolism in normal pregnancy having been described it will be shown in this paper that in toxaemia of pregnancy a more or less distinct alteration in histidine metabolism is to be found.

Experimental procedure.

Qualitative and quantitative estimations of histidine were carried out with the modified reaction of Kapeller-Adler.[2] A brief description of this method may be given. It is always preferable to use 24-hours specimens of urine for the test, but as it was not always possible to obtain a whole day's output from the pregnant woman, the investigations were made on the

urine that was first passed in the morning, having a specific gravity of about 1015 to 1025.

Reagents.

(*a*) Bromine reagent: 5 c.c. bromine and 500 c.c. glacial acetic acid were diluted with 1,000 c.c. distilled water, and the mixture stored in a brown glass bottle.

(*b*) A mixture of ammonia and ammonium carbonate: 400 c.c. ammonia solution, specific gravity 0.880, was mixed with 200 c.c. of a 10 per cent ammonium carbonate solution.

(*c*) Potassium iodide starch paper.

(*d*) N/10 potassium permanganate solution.

(*e*) 10 per cent sulphuric acid.

Technique.

The urine is filtered if necessary, and then tested with litmus paper. Acid urines can be directly tested for histidine, but alkaline urines must first be treated with potassium permanganate in sulphuric acid solution.

Treatment of acid urines.

To 5 c.c. of acid urine sufficient bromine reagent is added to change the original colour of the urine to orange-red, then to orange-yellow and finally to pale yellow. The latter colour indicates the necessary slight excess of bromine. This excess is tested for by potassium iodide starch paper; the fluid is then left for about 5 minutes during which the excess of bromine disappears, as confirmed by dropping it on the potassium iodide starch paper; 0.5 c.c. of the mixture of ammonia and ammonium carbonate solution are then added to the urine, now bromine-free. This fluid which shows a pH4 is shaken and the test tube containing it is placed in a beaker of boiling water for 2 or 3 minutes. In urines containing histidine a red or a reddish-violet colour appears. After some time the fluid deposits brown-black amorphous flakes of the dye. Urines free of histidine do not change their colour.

Treatment of alkaline urines.

To 5 c.c. of urine 2 c.c. 10 per cent sulphuric acid and sufficient N/10 potassium permanganate are added to change the urine to a pink colour, which will persist for half to one minute. The urine is allowed to stand for a few minutes until it becomes

clear and almost colourless, when a few drops of the bromine reagent are added until the fluid becomes pale yellow. The urine should then be tested with potassium iodide starch paper for a slight excess of bromine. The fluid is left for 5 minutes during which time the excess of bromine disappears. One c.c. of the mixture of ammonia and ammonium carbonate are added, the fluid (pH_4) shaken, and placed in a beaker with boiling water for 2 or 3 minutes. The urines containing histidine become red, while the histidine-free urines remain yellow. The importance of the preliminary treatment of alkaline urines with N/10 $KMnO_4$ in sulphuric acid solution for the achievement of satisfactory results may be illustrated by the fact that in many alkaline urines of pregnant women negative histidine tests were obtained, whereas the same urines showed positive reactions when treated with N/10 $KMnO_4$ before the determination of histidine.

For the *quantitative estimation* of histidine the urine must be filtered, after which the test is performed, as described above, according to the reaction of the urine on litmus paper. The quantitative measurement is carried out by means either of the colorimeter, Klett, or of the Stufen-photometer Zeiss,[11] or with the Spekker photoelectric absorptiometer. It is necessary to make quick readings before the separation of the dye in flakes begins to take place.

As already mentioned, the colour reaction, which is sometimes obtained with the urine of women who are not pregnant, differs from the ordinary positive reaction in healthy pregnant patients in that a persistently clear violet-blue colour is produced, whereas in the reaction of normal pregnancy a deep red or reddish-violet colour is produced in which brownish or black flakes of the dye are soon deposited.

Finally, it should be stressed that reactions with only a faint pink colour are to be considered negative.

Investigations of cases of toxaemia of pregnancy.

The 59 cases to be described fall into 4 groups according to the symptoms exhibited. (Paras. I to IV, pages 149 to 154.)

I. Cases of Hyperemesis Gravidarum

Symptoms: Fast pulse-rate, low blood-pressure, sometimes albuminuria. Five patients were investigated.

All data obtained are summarized in Para. I.

The patients of this group were between the 8th and 14th

weeks of pregnancy. All women exhibited a rather low blood-pressure, and sometimes had a pulse-rate over 100. Special attention may be drawn to patient No. 4, who had severe sickness from the 5th week and who had a very low blood-pressure. During the early months of her first pregnancy she had also suffered from excessive vomiting.

The histidine excretion in the urine of patient No. 1 was below the normal level, whereas in the remaining cases normal positive results were achieved.

II. Cases of Mild Pre-Eclamptic Toxaemia

Symptoms: Traces of albumin in the urine, slight rise in blood-pressure, oedema, headache, and heartburn. Twenty-six patients were investigated.

The patients of this group exhibited only a few symptoms of toxaemia of pregnancy. Slight oedema and sporadic headache could be noted, the blood-pressure was not generally high, and either albumin was absent from the urine or there were only traces thereof. Some of the patients had suffered from morning sickness in the first months of pregnancy; 17 of the 26 were primigravidae. Most of the patients were in the 8th or 9th months of pregnancy when the investigations were carried out. In the majority of cases the histidine excretion proved to be normal. The amount of histidine found in the urine of 3 patients (Nos. 3, 11, 12) was subnormal, and in 3 other cases (Nos. 2, 4, 5) only traces of histidine were recovered. Some cases (Nos. 2, 20, 25, 26) are of interest in that on one day only traces of histidine were excreted by the patients, to be followed on the next day by a rise to the normal level.

Analysing the findings in this group as a whole, one observes that the deviation of the histidine excretion from the normal level of pregnancy is slight.

III. Cases of Moderate Pre-Eclamptic Toxaemia.

Symptoms: Albuminuria, high blood-pressure, oedema. Fourteen patients were investigated.

In the cases investigated hypertension was mostly persistent, albumin was always to be found in the urine and nearly all patients showed oedema. Nine women were primigravidae. The patients were in the 8th or 9th months of pregnancy when they were admitted to the hospital. Two of the women exhibited visual disturbances (Nos. 2, 11), and 3 suffered from

breathlessness on exertion (Nos. 10, 11, 14). One patient (No. 9) complained of epigastric discomfort. There was one twin pregnancy (No. 13) and one stillbirth (No. 12). Two of the patients (Nos. 3, 7) had had morning sickness during the first months of pregnancy. In all the cases of this group the histidine excretion was below the normal level, and in several only traces of histidine were found. In one case (No. 1) the Aschheim-Zondek reaction was carried out and gave a positive result, whereas only traces of histidine were found.

Case No. 12 may particularly be discussed. This patient showed only mild clinical signs of toxaemic pregnancy so that it appeared to be doubtful whether she was a case of pre-eclamptic toxaemia. But her histidine excretion in the urine, investigated daily for a fortnight, was extremely low and suggested that it might be a case of serious pre-eclamptic toxaemia. As will be shown later, the urine of this patient contained, in fact, a fairly high amount of a toxic compound. It is noteworthy that this woman had a stillbirth, the child being born slightly macerated.

Case No. 14 is also of some interest. This patient, who became increasingly dyspnoeic from the 6th month of pregnancy, did hardly show any clinical signs of toxaemic pregnancy. Her histidinuria pointed, however, to the likelihood of a toxaemia of pregnancy. As an organic lesion of the heart could be excluded by a thorough examination, the dyspnoea of the patient was presumably due to toxaemic conditions in pregnancy.

IV. Cases of Severe Pre-Eclamptic Toxaemia

Symptoms: Hypertension and albuminuria persisting, oedema. Fourteen patients were investigated.

Para. IV shows that 9 out of 14 patients were primigravidae and one was pregnant for the 6th time. In all the patients a marked and persistent hypertension was observed, large amounts of albumin were found in the urine, and the majority complained of oedema. The patient pregnant for the 6th time (No. 3) had also epigastric pain and vomiting, severe cough, breathlessness and cyanosis. She had had renal trouble 6 and 4 years prior to this pregnancy. Two women with severe toxaemia (Nos. 10, 11) did not give any evidence of oedema. Four patients (Nos. 5, 10, 12, 14) suffered from severe headache, 2 (Nos. 5, 14) exhibited ocular disturbances and several were troubled by sickness (Nos. 3, 8, 10, 12, 14). There was one stillbirth (No. 1), one miscarriage (No. 9), one twin

pregnancy (No. 2), 7 cases of premature delivery (Nos. 3, 5, 8, 10, 11, 13, 14) and 4 cases of artificial delivery (Nos. 10, 11, 13, 14). In case No. 5 there were post-partum convulsions in both the mother and the child. Patient No. 14 developed eclampsia, and that was the reason for the induced delivery. Patient No. 10 had to undergo an artificial delivery on account of cardiac failure. Patient No. 11 developed thrombosis, hemiplegia, and aphasia, and labour had to be induced for that reason. Four patients (Nos. 3, 5, 10, 14) gave a history of toxaemic symptoms in their preceding pregnancies.

It is to be noted that most of the patients of this group had to attend the hospital at an earlier stage of pregnancy than the patients in groups II and III: namely between the 7th and 8th months of gestation.

In all cases in this group histidine was absent, or only traces of it were found in the urinary tests made at frequent intervals over a period of weeks. The absence of histidine excretion was always associated with considerable hypertension and marked albuminuria. So constant were these findings that a marked diminution in histidine excretion, or absence of histidinuria, can be used as a diagnostic sign of severe toxaemia of pregnancy.

It is of interest that the Aschheim-Zondek reaction* in 6 cases (Nos. 2, 3, 8, 9, 10, 11) gave either a positive or a weak positive result. A negative Aschheim-Zondek reaction was not obtained in any case, which indicates that even under toxaemic conditions gonadotropic hormones continue to be excreted, although sometimes at a reduced level. The reaction of histidine made simultaneously was mostly negative.

It will be demonstrated later than in cases of severe toxaemia of pregnancy changes in the histidine metabolism take place which explains why histidine does not appear in the urine. The lack of histidine in such cases is generally associated with severe albuminuria and other symptoms of profound toxaemia, and can itself be regarded as a salient feature of the condition.

It may be pointed out that improvement in the toxaemia of pregnancy is always accompanied by an increase in histidine elimination, so that the reappearance of histidine in the urine of patients with toxaemic symptoms may be considered a favourable sign.

* The author desires to thank Miss Mairi Mackay, Institute of Animal Genetics, Edinburgh, for numerous Aschheim-Zondek reactions carefully carried out by her.

Summary.

Histidine is a constituent of the urine throughout normal human pregnancy, the excreted amounts ranging between 15 and 50 mgm. per cent. Histidinuria is not appreciably affected in cases of mild pre-eclamptic toxaemia, but is considerably diminished in patients with serious symptoms of pre-eclamptic toxaemia. In cases of severe pre-eclamptic toxaemia histidine is not to be found in the urine, or only traces are found. So constant are these findings that a marked diminution, or total absence of, histidine excretion can be used as a diagnostic sign of severe toxaemia of pregnancy.

I. Cases of Hyperemesis Gravidarum

Patient No. 1. 0-para, 10th week of pregnancy; blood-pressure, 120/80; pulse-rate, never above 90; vomiting, from week before admission; albumin, +, trace, 0, trace; histidine mgm. per cent, 5, 7, trace, 8, 3, trace, trace; one miscarriage 18 months previously.

Patient No. 2. 0-para, 10th to 12th weeks of pregnancy; blood-pressure, 120/100, 110/60; pulse-rate, 88, 100, 88, 88, 80; albumin, +++, ++, ++, 0, trace, trace; histidine mgm. per cent, 15, 20, 12, 20, 20, 19, 22, 20, 20, 20, 15, 20, 18.

Patient No. 3. 1-para; 12th to 14 weeks of pregnancy; blood-pressure, 118/70; pulse-rate, 72, 80, 80, 84; vomiting, from 10 days before admission; albumin, 0, 0, 0; histidine mgm. per cent, 20, 15, 16, 20, 22, 12, 18.

Patient No. 4. 1-para; 8th to 10th weeks of pregnancy; blood-pressure, 100/70, 98/65, 80/55, 90/70, 95/75; pulse-rate, 80, 88, 90, 92, 80, 76, 96, 88, 84; severe sickness from 5th week of pregnancy; albumin, 0, 0, 0, 0; histidine mgm. per cent, 10, 15, 10, 30, 28, 12, 30. First pregnancy 10 years ago with excessive vomiting in early pregnancy as complication.

Patient No. 5. 3-para; 8th week of pregnancy; blood-pressure, 110/80; pulse-rate, 88, 82, 104, 98, 88, 88, 84; sickness from 6th week; albumin, trace, 0, 0; histidine mgm. per cent, trace, 20, 12, 15, 20, 16. First pregnancy, 1934, duration, 7 months. Hyperemesis as complication. Second pregnancy, 1935, duration 6½ months. Cause of abortion unknown. Third and 4th pregnancies were normal.

II. Cases of Mild Pre-Eclamptic Toxaemia

Patient No. 1. 0-para; 8th month of pregnancy; blood pressure, 158/110; slight oedema; albumin, 0, 0, 0, 0; histidine mgm. per cent, 40, 30, 40, 40, 32.

Patient No. 2. 3-para; 8th month of pregnancy; blood-pressure, 180/80; 110/60; oedema, feet and ankles, from 5th month; headache, when admitted; visual disturbances, occasionally black spots; albumin, 0, 0, 0; histidine mgm. per cent, trace, trace, 30.

Patient No. 3. 2-para; 8th month of pregnancy; blood-pressure, 170/90, 110/80; oedema, ankles for last 2 months; headache, during early months; albumin, 0, 0, 0; histidine mgm. per cent, 15, 10, 10; complained of fatigue and dyspnoea on exertion. Did not feel well throughout pregnancy.

Patient No. 4. 4-para; 9th month of pregnancy; blood-pressure, 140–150/80; oedema, absent; headache, absent; albumin, 0, +, 0; histidine mgm. per cent, trace, trace.

Patient No. 5. 0-para; 9th month of pregnancy; blood-pressure, 140/80, 120/75; oedema, ankles, and face for the last 2 months; albumin, 0, 0, 0, 0; histidine mgm. per cent, 10, trace, trace, 6.

Patient No. 6. 0-para; 9th month of pregnancy; blood-pressure, 145/90, 130/80, 130/80; oedema, absent; albumin, 0, 0, 0; histidine mgm. per cent, 20, 14, 15.

Patient No. 7. 0-para; 9th month of pregnancy; blood-pressure, 150/80; oedema, slight; headache, slight; sickness during the first 3 months; albumin, 0, 0, 0, 0; histidine mgm. per cent, 28, 25, 22, 20, 25, 25, 24.

Patient No. 8. 0-para, 9th month of pregnancy; blood-pressure, 100/60; oedema, slight; albumin, 0, 0, 0; histidine mgm. per cent, 26, 20, 24, 26, 20, 25.

Patient No. 9. 4-para; 8th month of pregnancy; blood-pressure, 120/80; oedema, feet; albumin, 0, 0, 0, 0; histidine mgm. per cent, 38, 35, 32.

Patient No. 10. 0-para; 7th to 8th months of pregnancy; blood-pressure, 160/100; oedema, ankles; headache, slight; albumin, trace, trace; histidine mgm. per cent, 20, 22, 18.

Patient No. 11. 0-para; 9th month of pregnancy; blood-pressure, 140/120, 120/80; oedema, ankles, face, hands; albumin, +, trace, 0, 0, 0, 0; histidine mgm. per cent, 8, 10, 10, trace, 8.

Patient No. 12. 0-para; 8th month of pregnancy; blood-pressure, 145/80, 130/70, 140/60, 160/90; oedema, ankles, from the 6th month; headache, +; albumin, +, trace, trace, +; histidine mgm. per cent, 8, 10, 12, 10, 13.

Patient No. 13. 1-para; 9th month of pregnancy; blood-pressure, 130/80, 130/80, 130/90; oedema, feet; morning sickness in the first months; albumin, trace, trace, +; histidine mgm. per cent, 28, 26.

Patient No. 14. 6-para; 7th to 8th months of pregnancy; blood-pressure, 150/100, 120/70; puffiness round eyes; albumin, trace, trace, trace, trace; histidine mgm. per cent, 35, 33, 25, 20, 30, 20, 20, 20, 25.

Patient No. 15. 1-para; 9th month of pregnancy; blood-pressure, 150/90; oedema, feet and ankles; visual disturbance, occasionally black spots; albumin, trace, trace, trace, trace, trace, trace; histidine mgm. per cent, 39, 32, 36, 39, 38; twin pregnancy.

Patient No. 16. 0-para; 9th month of pregnancy; blood-pressure, 130/80; oedema, feet, hands, face; albumin, trace, 0; histidine mgm. per cent, 12, 26, 25; Aschheim-Zondek reaction, weak positive.

Patient No. 17. 0-para; 7th month of pregnancy; blood-pressure, 140/80; 120/70; oedema, feet and legs from the 5th month; albumin, trace, 0, 0, 0; histidine mgm. per cent, 25, 30, 29, 28, 29, 31, 25, 25, 31, 29, 24.

Patient No. 18. 1-para; blood-pressure, 160/100, 170/110, 160/100; nausea; albumin, 0, 0, 0; histidine mgm. per cent, 30, 20, 34, 31, 25, 31, 26, 34, 42, 40, 37, 30.

Patient No. 19. Blood-pressure, rising slightly; albumin, trace, trace, histidine mgm. per cent, 20, 18, 15.

Patient No. 20. 0-para; 9th month of pregnancy; blood-pressure, 140/80, 120/65; oedema, ankles; slight morning sickness in the first 3 months; albumin, trace, trace, trace; histidine mgm. per cent, 10, 18, trace, 24.

Patient No. 21. 0-para; 5th month of pregnancy; blood-pressure, 130/75; vomiting, once, 4 days before admission; albumin, 0, trace; histidine mgm. per cent, 14, 20, 16, 12, 30, 30, 28, 24.

Patient No. 22. 0-para; 9th month of pregnancy; blood-pressure, 125/85, 180/130, 130/95; oedema, ankles, gradually increasing; albumin, +, +, trace; histidine mgm. per cent, 16, 10.

Patient No. 23. 0-para; 8th month of pregnancy; blood-pressure, 120/90, 120/80; albumin, +, +; histidine mgm. per cent, 40, 45.

Patient No. 24. 0-para; 9th month of pregnancy; blood-pressure, 155/105; albumin, 0, 0; histidine mgm. per cent, 18, 16.

Patient No. 25. 0-para; 9th month of pregnancy; blood-pressure, 130–140/80–100; oedema, slight, face, hands, legs; albumin, +, +, +, +, +, +, +; histidine mgm. per cent, trace, 25, 19, 25, 22, 30, 18, 22, trace, 25, 20, 22, 25, 30, 26, 20, 25, 20, 22, 15.

Patient No. 26. 0-para; 9th month of pregnancy; blood-pressure, 130–140/100–105; severe sickness absent during first 5 months; albumin, trace, trace, trace; histidine mgm. per cent, 0, 18, 5, 22, trace, 26, 8, 22, 5, 16, trace, 20, 18, 22, trace, 22, 5, 22, 15, 18, 0, 16.

III. Cases of Moderate Pre-Eclamptic Toxaemia

Patient No. 1. 0-para; 9th month of pregnancy; blood-pressure, 180/120, 140/100; oedema, ankles, 2 months before admission; some vomiting; albumin, +, +, ++; histidine mgm. per cent, 10, trace, trace, 11, trace, trace, trace, 4, trace, trace; Aschheim-Zondek reaction, positive.

Patient No. 2. 4-para; 8th month of pregnancy; blood-pressure, 180–200/120–140; 160/100; 160/100; oedema, feet and ankles; black spots in face and eyes; albumin, +, ++, +++, ++; histidine mgm. per cent, 5, 4, trace, 5, 8, 4.

Patient No. 3. 0-para; 7th month of pregnancy; blood-pressure, 140/80; 140/80; oedema, feet, last 4 weeks before admission; swelling of the vulva, +++; headache in the 4th and 5th months; morning sickness during the first 3 months albumin, +, ++, ++, ++; histidine mgm.

per cent, 6, 5, 5, trace, trace, 7, 6, trace, trace, trace, trace, trace, 6, 9, trace, trace.

Patient No. 4. 0-para; 8th month of pregnancy; blood-pressure, 140/90, 120/80, 145/100, 130/100; oedema, ankles, 2 months before admission; albumin, 0, trace, +, +; histidine mgm. per cent, 10, 10, 12, 9, 7, 12, 10, trace, 5, 7.

Patient No. 5. 2-para; 9th month of pregnancy; blood-pressure, 125/75; albumin, +, +; histidine mgm. per cent, trace, trace.

Patient No. 6. 0-para; 9th month of pregnancy; blood-pressure, 140/90, 140/90; some oedema of ankles; albumin, ++, +++, ++, ++; histidine mgm. per cent, 12, trace, trace, trace, 6, 6, trace, 15, 10, 8, trace, 6; heartburn, ++.

Patient No. 7. 0-para; 8th month of pregnancy; blood-pressure, 146/110, 140/90; vomiting, during first 4 months; albumin, +++, ++, ++,+, +++; histidine mgm. per cent, 8, 7, 9, trace, 5, trace.

Patient No. 8. 0-para; 8th month of pregnancy; blood-pressure, 140/100, 140/90; oedema, face, ankles, legs; albumin, ++, trace, trace; histidine mgm. per cent, 12, trace, trace, 12.

Patient No. 9. 0-para; 9th month of pregnancy; blood-pressure, 155/100, 145/100; oedema, +++, ankles, face, hands; nausea; albumin, trace, trace, histidine mgm. per cent, 5, 9; epigastric discomfort.

Patient No. 10. 4-para; 9th month of pregnancy; blood-pressure, 120/70, 110/80; oedema, +++, ankles, abdominal wall; albumin, trace, trace; histidine mgm. per cent, trace, trace. Breathlessness on exertion from the 6th month.

Patient No. 11. 3-para; 8th month of pregnancy; blood-pressure, 130/80, 150/90; oedema, ankles; severe blurring of vision; albumin, trace, trace; histidine mgm. per cent, 10, trace; 1 miscarriage; frequent attacks of epistaxis; breathlessness on exertion.

Patient No. 12. 0-para; 9th month of pregnancy; blood-pressure, 140–150/90–110; albumin, trace, ++, +,+, ++, ++; histidine mgm. per cent, 15, 12, 10, trace, trace, 6, 7, 3, 5, 5, 5, 0; stillbirth, child slightly macerated.

Patient No. 13. 4-para; 9th month of pregnancy; blood-pressure, 140/100; oedema, feet, ankles; albumin, +++, +++; histidine mgm. per cent, trace, trace; twin pregnancy.

Patient No. 14. 0-para; 9th month of pregnancy; blood-pressure, 140/90, 120/90; oedema, ankles; albumin, +, trace, +, ++; histidine mgm. per cent, 15, trace, 10, trace, 10, trace. Increasingly dyspnoeic from the 6th month, only on exertion.

IV. Cases of Severe Pre-Eclamptic Toxaemia

Patient No. 1. 3-para; 8th month of pregnancy; blood-pressure, 145/95; albumin, ++, ++, ++; histidine mgm. per cent, trace, trace, trace, trace; stillbirth.

Patient No. 2. 0-para; 9th month of pregnancy; blood-pressure,

155/110; oedema, for last 6 weeks; albumin, +++, +++; histidine mgm. per cent, 5, 0; Aschheim-Zondek reaction, positive; twin pregnancy.

Patient No. 3. 6-para; 7th month of pregnancy; blood-pressure, 180/120, 180/120; oedema, ankles, legs, sacrum, for last 4 months; vomiting, +; albumin, ++, ++, ++, ++; histidine mgm. per cent, 5, trace, 0, trace. Kidney troubles 6 and 4 years ago. This pregnancy, epigastric pain, breathlessness, cyanosis; Aschheim-Zondek reaction, +; premature delivery.

Patient No. 4. 0-para; 8th month of pregnancy; blood-pressure, 160/90, 130/80; oedema, ++, ankles, feet; albumin, trace, trace, trace; histidine mgm. per cent, 8, 10, 7, 7, trace, 8, trace, 8, trace, trace, 5, 6, 8, 8, 10, 10, 6, trace, 5, 8.

Patient No. 5. 0-para; 6th to 7th months of pregnancy; blood-pressure, 150/110, 140/110; slight oedema in ankles and face. Headache during the 4th month of pregnancy; subjective eye disturbances; albumin, ++, +++, ++, ++; histidine mgm. per cent, 0, 0, trace, 0, 5, trace, trace, 0, trace, 0, 5, 7, trace, 0; 1 miscarriage; premature birth. After delivery patient and child had convulsions.

Patient No. 6. 0-para; 8th to 9th months of pregnancy; blood-pressure, 140/100, 120/80, 145/100; slight oedema; albumin, ++, +++, +++, +++, +++; histidine mgm. per cent, trace, trace, 0, trace, trace, trace, 0, 0, trace, trace, trace.

Patient No. 7. 0-para; 8th month of pregnancy, blood-pressure, 180/120, 140/100, 140/100; oedema, ++; albumin, +++, +++, +++, +++; histidine mgm. per cent, 0, 0, trace, 0, trace, 0, 0, 0, trace, trace, trace, trace, 0, trace, 0, 0, trace.

Patient No. 8. 1-para; 7th to 8th months of pregnancy; blood-pressure, 150/110, 196/110; oedema, ankles; vomiting during the 2nd month; albumin, +++, +++, +++, ++, +++; histidine mgm. per cent, 0, 0, 0, trace, trace, trace, 0, 0, 0, 0; Aschheim-Zondek reaction, weak +; premature birth.

Patient No. 9. 0-para; 7th month of pregnancy; blood-pressure, 210/100, 190/120; oedema, feet, face; albumin, +++, +++, +++, histidine mgm. per cent, 10, 5, 7, 6, trace, 5, trace, trace, 0, 0, 0; Aschheim-Zondek reaction, weak +; 6 months' foetus, dead.

Patient No. 10. 1-para; 5th month of pregnancy; blood-pressure, 170/120, 160/100, 140/90, 140/90, 120/80, 140/100, 180/120; headache, +; sometimes feeling of nausea; albumin, trace, trace, trace, ++, +++, +++, +++, +++, +++, ++, +++; histidine mgm. per cent, 10, 6, 5, 7, 6, 0, trace, 0, trace, trace, trace, 0, 0, trace, 0, 0, 0, 0, 0, 0, trace, 0, 0, 5, trace, 5, 10, 0, 15, 0, 0, 0, 0, 0, 0, trace, trace, 0, 0, 0, 0, trace, trace, 0, 5, 7, 7, 0, 0, trace, 0, 0, 0; Aschheim-Zondek reaction, weak +. Two years ago premature birth following pre-eclamptic toxaemia; child was alive. One year ago abdominal hysterotomy because of a severe pre-eclamptic toxaemia; blood-pressure, 220/140; albumin +++. Miscarriage in the 5th month. This pregnancy, premature artificial delivery; heart failure.

Patient No. 11. 0-para; 8th month of pregnancy; blood-pressure, 150/100, 190/110, 130/70, 170/100, 190/130, 220/130, 180/110; oedema, absent; albumin, +, +, ++, +++, ++; histidine mgm. per cent, 0, 0, trace, trace, 0. Aschheim-Zondek reaction, extremely weak +. Thrombosis, hemiplegia, aphasia; artificial delivery, premature.

Patient No. 12. 0-para; 9th month of pregnancy; blood-pressure, 170/100, 140/85, 150/100, 140/100, 150/85; oedema, ankles, ++. Headache during the first 2 to 3 weeks. Slight giddiness and faintness. Morning sickness during the first 3 months. Albumin, +++, solid, +++, +++, +++; histidine mgm. per cent, trace, 0, 0, 0. General lassitude and tiredness.

Patient No. 13. 0-para; 8th month of pregnancy; blood-pressure, 160/110, 170/120, 180/130, 220/160, 200/160; oedema, ankles; albumin, +++, ++, ++, ++++; histidine mgm. per cent, trace, 0, 0; premature birth; classical Caesarean section.

Patient No. 14. 2-para; 7th to 8th months of pregnancy; blood-pressure, 180/100, 140/90, 160/100, 175/110; oedema, ++, feet, hands, face. Severe headache; blurring of vision. Morning sickness during first 3 months. Albumin, solid, ++++, solid, solid; histidine mgm. per cent, 0, 0, 0; 2 miscarriages. This pregnancy, in the 3rd month, threatened abortion cleared up. Has not felt well during all the pregnancy; patient developed fits; delivery induced; premature child.

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The significance of the Isolation of Histamine from the Urine in the Toxaemia of Pregnancy

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As the result of the findings obtained in the course of the investigation described in the preceding paper, the conclusion was drawn that toxaemic pregnancy is associated with abnormal histidine metabolism. It appeared to be possible that in severe toxaemia the histidine, instead of being excreted as such, was being transformed into some other compound, probably one of pharmacological activity.

Considering the chemical structure of histidine, the possibility of a transformation of this inactive substance into the very active substance histamine became obvious. Therefore, repeated attempts were made to detect this active compound in toxaemic pregnancy urine. The detailed description of these attempts is given in a paper at present in the press.[1] The results of these experiments may be summarized as follows. Four attempts have been made to demonstrate the isolation of histamine from the urine of women with various signs of toxaemia of pregnancy. In the first two experiments only fractions of a milligram of histamine diflavianate were isolated from 23 litres of urine from patients with severe pre-eclamptic toxaemia. A third attempt yielded 2.7 mgm. of histamine dipicrate out of 32 litres of urine from 2 women with very severe pre-eclamptic toxaemia (compare Para. IV, Nos. 10 and 11 of the preceding paper). In the fourth experiment with a modified technique 10.9 mgm. histamine diflavianate were isolated from 3 litres of urine from a woman suffering from severe hyperemesis gravidarum (compare Para. I, No. 1). From 39 litres of normal pregnancy urine with normal histidine excretion a detectable quantity of histamine could not be obtained. Since then two further attempts at isolation of histamine have been made with the modified technique. In a second case of hyperemesis gravidarum 34.6

mgm. histamine diflavianate were isolated out of 7,700 c.c. of urine. The second experiment was carried out on the urine of a woman with serious pre-eclamptic toxaemia, with the result that 62.5 mgm. histamine diflavianate were prepared from 8,500 c.c. of urine (compare Para. III, No. 12). It may be recalled that this patient exhibited only very mild signs of toxaemia of pregnancy, but demonstrated either a very low histidine excretion or entire absence thereof, and that her pregnancy terminated in a stillbirth, the child being slightly macerated.

There is no doubt that the histamine isolated from urine in cases of the toxaemia of pregnancy can have only been derived from histidine which is normally present in large amounts throughout pregnancy. The way in which histamine may be formed from histidine is extensively discussed in the paper mentioned above.[1] Two factors seem to be responsible for the rapidity of formation of histamine in the histidine metabolism, namely, the activity of two enzymes, (*a*) histidine decarboxylase, (*b*) histaminase. Animal tissues, especially the kidneys, contain both enzymes. Whereas the histidine decarboxylase, which can alter histidine to histamine, appears to be more effective in an atmosphere lacking oxygen than in the presence of oxygen (Werle[2]), the histaminase, an enzyme tending to the destruction of histamine, works only if oxygen is present (Best[3]). Recently Werle[4] reports that the activity of both enzymes is not only dependent on atmospheric conditions but also on the presence of various inactivators which regulate their action. It may be suggested that the occurrence of histamine in the metabolism of pregnant women will finally be determined by the balance in the activity of the histidine decarboxylase and the histaminase.

The occurrence of histamine in the urine in toxaemia of pregnancy having been proved, the possible significance of that finding for the pathogenesis and course of that disease may be discussed.

First of all it must be pointed out that the term toxaemia of pregnancy should be retained, since, for the first time, a real toxin has been isolated from the urine of toxaemic pregnancy. This is contrary to certain authors, notably Irving,[5] Seitz[6] and v. Jaschke,[7] who reject the assumption of a toxin as the cause of eclampsia. The fact that histamine has been isolated from the urine of patients suffering from pre-eclamptic toxaemia, as well as from the urine of women suffering from hyperemesis gravidarum, suggests that pre-eclamptic and eclamptic toxaemia, tox-

aemic vomiting and the premature separation of the placenta may not represent independent diseases, but may form only different manifestations of the same disease, probably of an intoxication by histamine. Although evidence has not yet been advanced as to the occurrence of histamine in normal pregnancy urine I am inclined to think that very small amounts of histamine may also be formed in the metabolism of normal pregnancy, and that the less pronounced symptoms like headache, morning sickness and dyspepsia occurring in nearly every normal pregnancy may indicate slight intoxication by histamine.

A comparison of the clinical picture in the various manifestations and degrees of toxaemia of pregnancy, together with the conditions produced by experimental intoxication by histamine, reveals numerous points in which there is a suggestive similarity. Injections of histamine in man produce a characteristic sequence of events, the intensity of which can be greatly reduced by giving the injections slowly and gradually. The changes produced are a slight acceleration of the pulse-rate, a slight fall in arterial pressure and a slight rise in the temperature—all of which may be observed in severe hyperemesis gravidarum. In addition a feeling of constriction in the head and headache are experienced, sometimes accompanied by visual disturbances (Best and McHenry[8]). Larger doses produce intolerable headache, vomiting and unconsciousness. Cyanosis and difficulty in breathing, particularly inspiratory dyspnoea, have also been recorded, and Kehrer[9] observed convulsions. Histamine injections also produce oedema, which is a common sign of pre-eclamptic toxaemia and eclampsia.

Histamine is also stated to increase the excitability of the sympathetic nervous system, and many obstetricians (e.g. Stroganoff,[10] Stander[11]) emphasize the presence of this feature in pregnancy toxaemia, particularly in hyperemesis.

In addition certain changes in the blood are common to both pregnancy toxaemia and histamine poisoning. Cyanosis in the latter has been mentioned, and anoxaemia is a recognized feature of pre-eclamptic toxaemia and eclampsia. In histamine poisoning the CO_2-combining power is lower, hyperglycaemia occurs, along with a decrease in the hepatic glycogen, and the sodium content and calcium content of the blood are diminished. All these changes have been claimed to occur in pre-eclamptic toxaemia and eclampsia, although it is notorious that the findings of different observers conflict in some measure.

Finally the pathological changes in various organs, particu-

larly in the liver and kidneys, in experimental intoxication with histamine so closely resemble those in toxaemic pregnancy that some authors (Hofbauer,[12] Heinlein[13]) conceived of histamine as the causative factor of eclampsia for that reason alone.

Whereas the decreased blood-pressure in cases of hyperemesis gravidarum is in accord with the known effect of histamine in lowering the blood-pressure, the hypertension characteristic of pre-eclamptic toxaemia appears at first glance to be at variance with it. It may, however, be recalled that histamine causes renal impairment and persistent albuminuria are mostly observed together with hypertension in cases of severe pre-eclamptic toxaemia. Since serious renal disturbances such as glomerular and tubular lesions follow histamine injections, it appears likely that the primary cause of hypertension in pre-eclamptic toxaemia may be renal impairment. This being granted, the rise in blood-pressure may occur as a protective measure, since it would seem to indicate an attempt on the part of the organism to maintain an adequate filtration pressure in the glomeruli. Thus, hypertension in pregnancy may provide, by its early appearance, a very important warning sign indicating the activity of histamine in the pregnant body.

A review of the literature as regards the aetiology of toxaemic pregnancy shows that, as already mentioned, some authors have considered histamine as the causative factor of eclampsia. Hofbauer[12] first suggested that histamine may be the cause of premature separation of the normally implanted placenta. He was, however, not able to give any convincing evidence with respect to the occurrence and the origin of histamine in toxaemia of pregnancy. Reference is also made by Revoltella[14] to the occurrence of histamine in the blood, urine and various organs of patients with eclampsia and pre-eclampsia, but he, also, did not advance further confirmation of this opinion. He assumed that histamine is either formed by the foetus or by the placenta itself, or derived from the intestine. As already mentioned, Heinlein also believed histamine to be the cause of eclampsia, but, again, he did not adduce any evidence in support of his belief.

An observation made by Edlbacher[15] should be mentioned here. This author reports that, according to his experiments, histidine, as well as arginine and cysteine, have been found to cause a complete inhibition of the customary action of histamine. In view of this observation it appears likely that the histidine occurring in larger amounts in normal pregnancy

may have a protective effect against histamine which may appear in the metabolism as an intermediate product. In cases of severe toxaemia, however, in which histidinuria is absent, that protective effect of histidine against histamine may be absent. In this connexion reference may be made to a paper of Walther,[16] who claims striking results from administering injections of histidine in various cases of vomiting and gastric disturbances in pregnancy. The gastric troubles, heartburn and vomiting, disappeared very quickly under that treatment.

Finally, with regard to the occurrence of histamine in toxaemia of pregnancy it may be recorded that eclampsia and vomiting are unknown in animals during pregnancy (Hofbauer,[12] Cruickshank,[17] Attlee[18]) but histidinuria and, of course, histaminuria are absent in pregnant animals.

Summary

1. It is suggested that histamine plays an important *rôle* in toxaemia of pregnancy.

2. The different manifestations of the intoxication with their different symptoms and events may finally depend on the pregnant woman herself, on her adaptability to the changed conditions, and on the state of nutrition of her body. Malnutrition may play its part since Feldberg[19] observed that a starved body is much less resistant to histamine than a well-nourished organism. The normal pregnant woman will more or less easily adapt herself to changes which result from the altered metabolism, and will soon overcome the trouble which perhaps small amounts of histamine, intermediately occurring, will inflict upon her. The sensitiveness of pregnant women towards histamine may vary with the individual. Hofbauer[12] found a marked difference in the sensitivity to histamine even in pregnant guinea-pigs.

3. The term toxaemia of pregnancy should be maintained, since a real toxin (histamine) has been found to be excreted in pathological pregnancy.

4. The significance of the isolation of histamine from toxaemic pregnancy urine is discussed.

5. The biological action of histamine is compared with the symptoms of toxaemia of pregnancy, and the opinion is expressed that histamine may be assumed to be a causative factor of that complex of disease.

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An Evaluation of the Treatment of Albuminuria of Pregnancy by the Water-balance method, assuming the Theory of Water Intoxication in Pregnancy

BY

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INTRODUCTION

IN 1932 a valuable paper by Dr. Arnold and Dr. Fay[1] on the Causes and Treatment of Eclampsia encouraged me to initiate the treatment recommended, according to the theory of water intoxication, in the management of patients suffering from albuminuria and so-called toxaemias of pregnancy under my care.

At that time I had been in charge of the maternity clinic at Walton Hospital for 4 or 5 years, which was then in the process of expansion, and the numbers of patients suffering from albuminuria in pregnancy being admitted for treatment were rapidly increasing. I had always felt that the semi-starvation treatment of albuminuria in pregnancy was unsatisfactory, because I believe, primarily, that starvation is the last form of treatment which the pregnant woman needs; secondly, that the renal condition in pregnancy is not the same as in Bright's disease; thirdly, because I know that albumin in the urine, if it does not come from the protein of food, will come from body metabolism; fourthly, as a student it was instilled into me that the loss of albumin, even if the urine becomes solid on boiling, is small compared with the body weight; and, lastly, that in any case the amount of albumin in the urine is no criterion of the degree of renal damage.

In the case of antenatal clinics, previously, in dealing with ambulatory patients whose condition was such that it did not necessitate admission to hospital, or more particularly with those who had been in hospital for investigation, and were subsequently discharged, I felt that instructions as to diet were rarely

carried out, and that the patients did not omit the proscribed articles of diet, in spite of careful explanations. Further, the majority of these patients are so poor that they often have to eat what they can get, and have little or no choice in diet, so that it is useless trying to lay down what they shall eat, and what they shall not.

The water-balance diet is much easier to regulate for ambulatory cases as there is only one *don't*, and that is with regard to the limit of the amount of fluid to be taken. The average woman does not feel it a hardship, or deprivation, to have her fluid intake cut down, because, as a rule, she takes a minimal quantity. Also, in dealing with fairly intelligent women, it is possible to get them to measure their own urinary output periodically so that they themselves can keep a check on their progress.

I believe that the simpler the method, the better for the uneducated type of patient with whom we have to deal, especially in the case of those patients who insist on going out of hospital while in an unfit state. The clinic being at a municipal hospital, the authorities are powerless to keep patients in if they really insist on being discharged, and the threat of refusing to readmit them for the confinement is, as they know very well, an empty one.

Dr. Chisnall, who was my house surgeon at that time, inaugurated the new system, and was awarded the M.D., Liverpool, for a thesis entitled, "The Effect of Fluid Limitation upon those Albuminurias of Pregnancy associated with Hypertension",[2] for work done on the early cases.

We thought the results of the treatment were so satisfactory that we have continued this method since, and in 5 years have treated 905 patients, and now report deliveries of 859, some of whom had repeated pregnancies.

Classification

Owing to the absence of a satisfactory method of classification, I have not made any attempt at separating these cases into groups under different heads.

Though they included all cases of albuminuria, which was the reason for investigation and treatment, the amount of albumin in itself was rarely, if ever, taken into account. There being no definite standard of abnormality in the level of the blood-pressure, cases could not be classified by this sign. The rough standard of the blood-pressure of any normal patient being the

age plus 100 is not sufficiently exact to use as the standard of normality in pregnancy, and as a basis for classification.

The syndrome of symptoms recognized as pre-eclampsia is definite enough in certain cases, but in others, some symptoms and signs are prominent while other, more common, ones may be lacking.

It is well recognized that pregnancy can give rise to renal damage in a patient who was previously quite normal—the so-called ' pregnancy kidney '. It is further realized that pregnancy may occur in a patient whose kidneys were damaged by previous disease or pregnancy, and this may be termed chronic nephritis with intercurrent pregnancy.

When, however, pregnancy has commenced to be associated after with symptoms of renal disease, it may be, and often is, impossible to decide as to whether the case belongs to the first or second group. Though at present the immediate treatment is the same, necessarily so, the differential diagnosis is of importance from the point of view of the further management of the patient, and still more so from the point of view of prognosis, both with regard to the patient's after health and subsequent pregnancies.

I know of no test which will differentiate the pregnancy kidney from that which is already in a damaged condition on which the strain of pregnancy is superimposed, the so-called chronic nephritis with pregnancy.

It is true that in the extreme stages of renal degeneration, tests such as the estimation of the non-protein nitrogen and blood-urea concentration will disclose the damaged renal condition, but I believe that slight and early stages may be present which are previously symptomless, and are brought to the fore by pregnancy, and may stimulate the pregnancy kidney.

In the early stages of this series of cases we were only concerned with the systolic and diastolic blood-pressure during the pregnancy, but later we noted as a routine the pressure during the lying-in period, and in a number of patients it was found that the blood-pressure remained at the same level as during the pregnancy, while in others the pressure rose sometimes to a new high level in the early days of the lying-in period. This new rise was not due to the strain and stress of labour, for it recurred in the patients who had the easiest of labours, and often in the multiparae, and the usual time was the 3rd or 4th day of the lying-in period.

I suspected these patients of being those with previous renal

damage, but beyond being able to demonstrate casts in the urine, the usual biochemical tests did not show any abnormality. In some classifications the term 'low kidney reserve' is used to explain an otherwise inexplicable albuminuria, often without symptoms or other signs. While I think that this term may be used for a primigravida, I cannot understand its being invoked to explain the symptomless albuminuria of a multipara when it is known that her previous pregnancies have been normal and free from albuminuria.

It seems to me that if, say, the sixth pregnancy is associated with albuminuria and the cause is said to be low renal reserve, then the previous 5 pregnancies should have been associated with albuminuria due to the same cause. Similarly, in a patient who has eclampsia with her first pregnancy and simply has a slight albuminuria with the second, without any rise in blood-pressure or other symptoms, I do not believe that the second case should be classed under the heading of low renal reserve.

In patients who have fits there is little difficulty in classification as eclampsia, though I think that the term eclampsia should be reserved primarily for the incidence of fits in the primigravida in which it is extremely likely that the pathology of the kidney is the pregnancy kidney, and that some other term, say 'uraemic convulsions', should be applied to the fits occurring in the multigravida who probably has had some renal damage previously either apart from, or during, a pregnancy.

With regard to the association between eclampsism and a raised blood-pressure, I feel that there is some other unknown factor at work in those patients who suffer from convulsions. The typical eclampsia occurs in the primigravida who has a raised blood-pressure with a large quantity of albumin in a diminished amount of urine, but occasionally a fit will occur, usually during labour, without any undue rise in the blood-pressure and amount of albumin in the urine.

In this series, cases of hyperemesis of pregnancy are not included for the reasons that they were treated in a different department, and, further, rarely have albuminuria as a primary sign.

Management of Cases of Albuminuria

Every case of albuminuria, whether slight or severe, in a primigravida or multipara, with or without other symptoms or signs, attending the antenatal clinic is pressed to come into hospital for investigation.

On admission, a specimen of urine is withdrawn by catheter, to eliminate vaginal and vulval sources of albumin and cells to confirm the presence of albumin, and for microscopic examination for blood-cells, organisms, and casts.

The patient is put to bed and kept there until some decision is made as to her condition, and the routine diet is given. (Table I.)

This diet is an ordinary mixed diet, and contains 20 ounces of free fluid, i.e. measured fluid in the form of milk, tea, cocoa, or coffee. Such fluid as moisture in meat and vegetables cannot be estimated.

After the first day in hospital the output of urine every 24 hours is measured, and includes an estimate of the fluid part of the faeces, if any, and is charted daily. (Table II.) The moisture in expired air and perspiration cannot be estimated. The number of daily movements of the bowels is noted, as an excessive number will alter the estimate of the amount of urinary output.

The balance is noted between the amount of fluid intake (20 ounces) and the amount of urinary output, and if the output is about the equivalent of the fluid intake—i.e., 20 ounces—the latter is maintained at that level for a time.

Arnold and Fay recommend that the amount of intake shall be guided by that of the output during the previous 24 hours. In practice, in the clinic, when dealing with a large number of patients, this was found to be impracticable, so the amount of intake, 20 ounces, was selected as a routine because it was seen to be the average amount of daily output and is easily divided up into equal parts.

The blood-pressure, systolic and diastolic, is estimated daily by the same observer at about the same time, and recorded on the same chart. (Table II.) The amount of albumin is estimated daily by Esbach's albuminometer, and also charted.

The main symptoms—headache, oedema, vomiting—and the presence of the foetal heart-sounds are also noted daily on the chart under the appropriate headings.

The previous history of the patient is carefully inquired into, particularly the pre-pregnancy history in a primigravida and the history of previous pregnancies if a multipara, to discover any suggestion of previous renal damage.

The dates and intervals between previous pregnancies are an important factor in the multipara, for I am sure that too frequent childbearing has a deleterious effect on the renal function.

The date of commencement of the present pregnancy is important, for on it may rest the decision as to further treatment. (See page 175, decision *re* induction.)

A history of the symptoms during the pregnancy under review is also of importance.

A careful examination of the patient is now to be made, both of the general and local systems.

In my experience, so many women are uncertain in the dates of their last menstrual period that careful examination of the pregnancy and comparison between its size and the supposed period of gestation should always be made, both from the point of view of timing the termination of the pregnancy and also of deciding as to the course to adopt in the interval.

The presence of oedema is a common and important sign, and it is sometimes difficult to decide whether oedema of the lower limbs is due to the renal dysfunction or to intra-abdominal pressure. Oedema due to pressure tends to disappear more rapidly than the so-called toxic oedema when the patient is kept in bed. In this respect the point noted by Gibbon FitzGibbon is very valuable, namely, that swelling of feet present in the morning necessitating the wearing of larger shoes than usual is very suggestive of toxic oedema. Generalized oedema of the abdominal wall is always due to renal dysfunction, but in the obese an area of fat and skin in the hypogastrium, which in the erect posture tends to overhang the symphysis pubis, often shows oedema which is attributable to the posture. Oedema of the face and other parts of the trunk can confidently be ascribed to renal disease. Visible oedema together with complaints of headache and vomiting, which are not common, as a rule rapidly improve and disappear under this regime.

Complaints of disability and disturbances of vision are not common and do not bear any relation to the physical signs. In many cases with marked functional optic defects ophthalmoscopic examination of the fundus oculi did not reveal anything abnormal, though this examination should be made as a routine.

In the great majority of patients this *régime* results in a lowering of the blood-pressure, with the diminution of the oedema and cessation of the other symptoms, and an increase in the amount of urinary output. In those patients in whom the blood-pressure is unaffected a tentative diagnosis of previous renal disease is made, and this is supported by the presence of hyaline and granular casts in the urine. If the blood-pressure is at a comparatively high level in consideration of the age of the

patient, or if it is actually above 200 mms. Hg systolic, intravenous injection of a hypertonic solution is practised. Arnold and Fay recommend both glucose and magnesium sulphate. I had already used magnesium sulphate in the treatment of eclampsia with good results, so I was biased in its favour, but in the early days we injected glucose 25 per cent and magnesium sulphate 20 per cent solutions indiscriminately, but lately, owing to the excellent results of the latter in the treatment of eclampsia, it has now almost entirely replaced the glucose injections. A practical point, which operates also in its favour, is that a smaller quantity, 10 c.c., of magnesium sulphate solution, which can be contained in a large syringe, is the correct dose, while that of glucose 25 per cent solution, 50 c.c., is more difficult to deal with.

Owing to the risk of dangerous depression of the respiratory system by magnesium sulphate, it is now our custom to inject with it 10 c.c. of calcium gluconate solution 10 per cent, which also has an effect as a hypertonic solution, and also, it is claimed, by virtue of the calcium element.

An injection of magnesium sulphate solution and calcium gluconate is thus given daily intravenously, so long as its effect is to cause falling of the blood-pressure until this is within normal limits. If, however, the blood-pressure does not appreciably diminish within 7 to 10 days the injections are discontinued, and in some cases a fall of blood-pressure then occurs.

When this treatment was first commenced, under the influence of the teaching which lays undue stress on the dangers of hyperpiesis, in the event of failure of the injections to lower the blood-pressure, it was the custom to recommend and practise the induction of premature labour. When, however, examination of the blood-pressure during the puerperium revealed the fact that the blood-pressure might never fall after delivery without any apparent ill-effects, at any rate immediately, inductions were not so readily recommended, and I think that in the early days more pregnancies were disturbed than was absolutely necessary and certainly more than are done now.

To-day the fact that the blood-pressure is high, unless it is persistently over 200 mms. Hg, does not *per se* persuade me to advise induction of labour.

Arnold and Fay recommend spinal puncture with complete drainage of cerebro-spinal fluid in these severe and persistent cases of hyperpiesia. I have not used it as a routine, but only occasionally as a preparation for the induction of abortion or

premature labour in an endeavour to prevent eclampsism associated with the onset of parturition, which is a recognized danger of this procedure in the circumstances. I prefer, however, the exhibition of morphine and the injection of magnesium sulphate and calcium gluconate as a prophylactic before the induction, which is usually by rupture of the membranes or by the introduction of a stomach tube.

I believe that the failure to establish a water balance between urinary output and water intake is much more serious than a failure to cause lowering of the blood-pressure. In the event of the output being consistently under the initial allowance of 20 ounces, the latter is diminished to 15 or 16 ounces as being the better amount, since it is more easily divided into four equal parts. If the balance is not soon established at this level then induction of premature labour is usually recommended.

Reduction of fluid intake to 16 ounces almost invariably gives rise to a complaint of thirst by the patient, and for that reason cannot be long maintained.

Only occasionally is there a complaint of thirst with a 20 ounces intake; it may be because women do not habitually take much free fluid. In the event of the output being consistently above the 20 ounces intake, the latter is increased to 30 ounces, and its effect on the output noted. If the output is similarly increased, the intake is then increased indefinitely, and if the blood-pressure is within normal limits the special chart is discontinued.

Medicinal Treatment.

In order to ensure a regular action of the bowels, these patients are given a small dose of magnesium sulphate, ʒii; magnesium carbon. pond., gr. xx; zinc. zingiber., ♏x; aqua menth. pip., ad ℥i; but an attempt to promote severe purgation is not made, since frequent actions of the bowels upset the estimation of water output, and, according to the theory of this treatment, are unnecessary.

Each patient receives a daily tablet of a mixture of vitamins, in order to combat puerperal sepsis, in the belief that the underlying cause of albuminuria predisposes to infection.

In those cases in which the laboratory report of the urinary examination is to the effect that pus cells and organisms are present, a mixture containing potass. citr. ʒi to ℥ss. is given. It has been suggested that urinary infection is a predisposing cause

of renal degeneration; and in our cases it is quite common to note the presence of pus cells and organisms in the urine, in association with this condition.

Many of these women are pale, and on investigation are found to be suffering from secondary anaemia. It is well recognized that albuminuria is associated with accidental haemorrhage, and for this reason alone the condition of the blood needs attention. A preliminary blood-count and estimation of the haemoglobin will give a guide as to the line of treatment. In markedly anaemic patients treatment is well started by a blood transfusion, followed up by injections of a liver extract and by massive doses of iron by mouth. The preparations I favour are Blaud's pill in increasing doses, or large doses of ferri et ammon. cit. I also believe in the efficacy of careful applications of small doses of ultra-violet light.

In the treatment of secondary anaemia, the possibility of hypochlorhydria must be remembered, and if suspected, the administration of hydrochloric acid commenced with the iron therapy.

Thyroid extract. The appearance of a number of these patients suggests the condition known as the 'large white kidney patient', and others are typical of myxoedema. If the former do not have the urinary findings to support the large white kidney diagnosis—i.e., a small quantity of urine with a large amount of albumin and casts—I recommend the administration of thyroid, as also in cases suggestive of myxoedema. I believe in commencing with gr. 1 thyroid extract daily, increasing to gr. 2 after a week, and so on; a weekly increase until a maximum of gr. 5 daily is being given. In the absence of signs of excess the dosage is maintained at this level until parturition occurs.

In those patients with excessive high blood-pressure, when it is believed that the only rational treatment is to empty the uterus, some attempt at reducing the blood-pressure should be made before attempting induction of abortion or labour, for fear of precipitating eclampsism, and this is best done by preliminary lumbar puncture before the operative procedure of induction, whichever method is chosen, and is followed by the routine treatment of eclampsia—i.e., the injection of morphia gr. $\frac{1}{4}$ and magnesium sulphate, 20 per cent, 10 c.c., intravenously

In some patients during this preliminary treatment eclampsia will at times supervene, and needs urgent treatment. In such I am convinced that the supervention of eclampsism in patients under treatment by this method is usually due to the onset of

labour, or the death of the foetus, and is more easily controlled than in patients not being so treated.

Intra-uterine death of the foetus gives rise sometimes to a marked rise of blood-pressure above the usual level, which is akin to the rise in pressure to which reference has been made, which sometimes follows parturition. This foetal death may not be appreciated until spontaneous or induced labour causes the expulsion of a macerated foetus.

If eclampsia supervenes without the onset of labour, the treatment of this condition must be instituted, and when the patient has recovered, induction of labour should be practised by an approved method. (See section on Induction.)

The Management of Eclampsia

It must be thoroughly understood and absolutely enforced that the patient must never be left alone except for the shortest possible space of time. She must be kept in bed in the Sims's posture in a darkened, quiet room. The room should not be so dark that a light needs to be flashed on for inspection, manipulation, or treatment, but a steady dim light in which it is possible to attend to the patient. The clanking of basins and buckets, and the rattling of utensils is to be avoided, but low-toned speech is not prohibited. During the time that fits are recurring, some form of gag should be *continuously* in the mouth. A sorbo-rubber ring pessary big enough to go in the mouth and under the chin will remain in position without any trouble. After the initial fit biting of the tongue or cheek should be regarded as a slur on the conduct of the attendants.

Catheterization at the outset, if the convulsions permit, is of value for purposes of examination of the urine, particularly the microscopic investigation, which may give a useful clue of the condition of the kidneys.

Treatment.

In the period before this conception of toxaemia was adopted and all the cases in the clinic were treated according to the water-balance theory, I believed in the conservative treatment of eclampsia by the preliminary injection of morphia, followed by intravenous injection of magnesium sulphate, and in 1933 published a short series of cases and the method of treatment.[3]

Following the commencement of the water-balance treatment to the intravenous injection of magnesium sulphate I added the

alternate injection of glucose solution, but after a short period tended to discontinue it, as I found that intravenous injections of magnesium sulphate are much more effective in combating the convulsions.

I think that the injections of magnesium sulphate should be continued until the convulsions cease, and instructions are laid down in the clinic that each fit shall be followed by an intravenous injection of magnesium sulphate.

Latterly the injection of 10 c.c. of calcium gluconate solution intravenously has been added to that of magnesium sulphate owing to the fear of respiratory depression by the latter, a fear which I believe to be greatly overrated, in the presence of such a fatal condition as eclampsia, because continuation of the eclamptic state almost inevitably leads to cerebral haemorrhage after which the fatal termination is certain.

One case, which recovered, received 5 injections of magnesium sulphate within 2½ hours and without any deleterious effects. Morphia gr. ½ is given at the commencement, with the first dose of magnesium sulphate, and gr. ¼ is given after half an hour if the fits recur during this time.

The further exhibition of morphia depends entirely on the progress of the case as to whether coma is present or not and whether parturition begins and is completed or not. In most cases I recommend that doses of morphia gr. ¼ should be given two or three times daily until the fear of recurrent fits may be said to be abated.

Chloral hydrate. This is a useful adjuvant to morphia but cannot replace it. The regular administration of chloral according to a time-table is recommended by Stroganoff,[4] but I believe in a dose of chloral hydrate gr. 30 at the commencement of treatment, by mouth if possible.

If the patient is comatose, or is vomiting excessively, and cannot retain any drug, this may be given by the rectum, but such administration must follow the colonic lavage, which may not be given immediately in the event of frequent and severe convulsions until the sedative effect of the morphia and magnesium sulphate is apparent. If the patient is able to take the chloral by mouth, gr. 30 may be given every 4 or 6 hours.

Chloroform. The administration of chloroform is imperative for those patients in whom severe fits frequently recur, possibly before the effects of the morphia and magnesium sulphate are established. It may be needed also for catheterization, colonic lavage examination, or delivery in those patients

who are especially irritable and tend to have convulsions when manipulations are being carried out.

Chloroform is said to be contra-indicated in this disease owing to its effect on the liver. I do not think it has any deleterious effect in the small therapeutic doses required, and in any event is to be preferred to ether, which is slower in action, requires a relatively greater amount, and has its notoriously irritating effect on the respiratory system.

The toxic action of chloroform on the liver cells is only produced by larger doses, and exacerbated by the presence of sepsis.

Coramine. This drug is a well-known cardiac tonic, and is only needed when cardiac failure commences, which is usually due to too frequent and uncontrolled fits.

Special Treatment.

Spinal drainage. There is no doubt that this is a valuable therapeutic measure, and is recommended for all deeply comatose patients whether they are having convulsions or not, and in those women who are conscious and complain of severe headache. In the former, whether it lightens the coma or not, it may be of use in prognosis, for if the fluid is bloodstained it probably denotes massive cerebral haemorrhage in which the prognosis is hopeless.

In cases in which the cerebro-spinal fluid is clear, lightening of the coma is to be expected, with improvement of the prognosis. Spinal puncture should be made at the lower border of the third or fourth lumbar vertebra, using a platinum iridium needle after the instillation of local anaesthesia 1 per cent novocaine in the skin and superficial fascia, and if thought necessary the inhalation of a few drops of chloroform. The patient must be kept lying on her side, and the spinal theca drained dry.

Venesection. This procedure is recommended in cases of cyanosis associated with engorgement of the right side of the heart and pulmonary oedema. It will seldom be found to be necessary if the fits are quickly controlled with morphia and magnesium sulphate in the early stages, for it is usually due to cardiac failure initiated by exhaustion as a result of excessive convulsions. It is not recommended, as heretofore, as a method of eliminating the toxins (*sic*) from the circulation.

For the purpose of venesection, the medium basilic vein is chosen, and this may be tapped by the insertion of a large

needle or incised and the blood allowed to drain directly into a vessel. The bleeding is facilitated by medium compression of the upper arm with a tourniquet, or, better, with the inflatable armlet of a sphygmomanometer.

Colonic lavage. This form of treatment is regarded as the mainstay of the therapeutic measure in some clinics. In my practice it is carried out when the condition of the patient, particularly as regards the number of fits and the irritable reaction to stimuli, is improving, for its main purpose is to clear the large bowel, having as its aim to stimulate the expulsive action of the uterus if present, and to prepare the pelvic canal for the second stage of labour just as in normal uncomplicated parturition.

Catheterization. Catheterization is always a necessary procedure in cases of slight and deep coma, and occasionally during the second stage of labour in conscious patients, though the amount of urine excreted is almost invariably small. In these cases also attention to the bladder is said to encourage uterine action and facilitate expulsion of the foetus in the majority of the patients who are in labour.

Gastric lavage. In my opinion this form of treatment is not to be lightly undertaken. At the best of times it is a distressing ordeal and should be reserved only for patients in deep coma associated with incessant vomiting, which is dangerous, in that it gives rise to the real danger of inhalation asphyxia. Passage of a stomach tube is not justifiable solely in order to introduce any special drug into that organ.

I think that a certain amount of vomiting is actually beneficial in those cases in which there is a tendency to pulmonary oedema, it being well recognized that the act of emesis has an expulsive action on foreign material in the smaller air passages.

Administration of oxygen. The presence of a cylinder of oxygen in the room is absolutely necessary. There is inevitably a measure of asphyxia and cyanosis associated with the convulsions, and it may be increased by cardiac failure and pulmonary embarrassment. It is useless giving oxygen during the tonic stage of the convulsion which is the most dangerous, as it cannot be inhaled, but it should be commenced during the clonic stage, thereby relieving the cyanosis produced by the previous phase.

Management of the pregnancy. In the event of labour being associated with eclampsia, as it is most frequently, the only care normally necessary is to ensure that the lie of the foetus is longitudinal. Labour as a rule is smooth and easy, the child being usually small and dead, owing to prematurity.

When the presenting part reaches the pelvic floor after full dilatation of the cervix, I believe in extracting the foetus, as we have found that convulsions are apt to be stimulated by the pains of the second stage of labour, and a foetus surviving till then may perish in the last stages of the labour due to the inevitable maternal asphyxia.

In the event of labour not commencing spontaneously, delivery is not hastened until the convulsions and associated eclamptic conditions of the patient have been relieved and her state is one of pre-eclampsia.

I have never performed a Caesarean section for eclampsia, and I do not think it is justifiable.

In the event of death of the foetus in the eclampsism, labour normally starts within 2 to 3 days, but if it does not, I believe in strongly advising the induction of labour, whatever the period of gestation. Induction of labour should be carried out in the simplest manner possible, and I recommend rupture of the membranes if the foetus is dead or too immature to survive, or by the introduction of a stomach tube, or bougies, if the foetus is alive and at or near term.

Copy of Instructions for House Surgeons and Nurses in the Treatment of Eclampsia at the Clinic

On Admission.

1. Give morphia gr. ½ and intravenous magnesium sulphate solution (20 per cent), 10 c.c., and calcium gluconate solution (10 per cent) 10 c.c. If the patient is conscious give chloral hydrate gr. 30 by mouth, and repeat every 4 hours.

2. If there is a fit within the first half-hour of above injection, give morphia gr. ¼, and repeat magnesium sulphate solution 10 c.c. and calcium gluconate solution 10 c.c.

3. Every time the patient has a fit repeat the dose of magnesium sulphate and calcium gluconate solutions, except if fits follow one after another, stop them by inhalation of a minimum quantity of chloroform.

4. If there is no fit within the first half-hour of the first injection, give morphia gr. ¼ at the end of the first hour.

5. In the presence of deep coma, or a complaint of severe headache, perform lumbar puncture, and drain the spinal canal dry.

6. In the presence of much cyanosis and oedema of lungs, consider venesection and atropine.

7. Catheterization is necessary in the presence of coma. Postpone rectal washout until the fits are well controlled, and do not give chloral by rectum until that has been done.

8. If fits are induced by catheterization and colonic lavage, control them with a minimum inhalation of chloroform.

9. Cardiac failure is to be treated with coramine.

10. Consider gastric lavage only in the presence of repeated vomiting when the patient is comatose.

11. If labour is in progress, ensure that the lie of the foetus is longitudinal. When presenting part is on the pelvic floor, the 2nd stage of labour may be completed by the forceps.

Nursing.

1. Darkened room.
2. Absolute quiet.
3. Sims's posture, especially if comatose.
4. Gag ready for use. If fits are frequent keep it in the patient's mouth continuously.
5. Prepare oxygen cylinder for administration.

Induction of Abortion and Premature Labour

I recommend and practise the induction of abortion in those patients in whom:

(1) The pregnancy has commenced within 12 months of a previous pregnancy which had been complicated by albuminuria and hyperpiesis, and especially eclampsia.

(2) Albuminuria and hyperpiesis arise before the 28th week of pregnancy.

(3) It is known that chronic renal damage existed before the pregnancy commenced.

(4) The foetus is known to be dead.

(5) In patients in whom ante-partum eclampsia has occurred, after curing the convulsive stage.

(6) When the patient first comes under notice after the period of viability of the foetus (28 weeks' gestation) under the following conditions:

(*a*) In those patients with a blood-pressure of 200 mms. Hg systolic and over.

(*b*) In those patients in whom a water balance is not maintained.

In all other cases regard is paid to the period of gestation, there being a tendency to delay induction until the later weeks of pregnancy in order to ensure a live birth if possible, for in those patients who carry the pregnancy up to 30 weeks at least without signs I do not think the subsequent prognosis is likely

to be affected by delaying the parturition. However, due regard is paid to the level of the blood-pressure and the effect of rest and treatment on the other physical signs and symptoms. I agree that the physical signs of oedema and hypertension in the optic fundi form a potent argument in favour of the induction of premature labour whatever the period of gestation.

As stated in the section on management, I do not now believe that persistence of a moderately raised blood-pressure, in spite of treatment, if other physical signs and any symptoms are improved, is an absolute indication for induction of premature labour.

In this question of whether to induce labour or abortion or not in relation to the period of gestation arises the importance of correlating the size of the pregnancy with the alleged period of gestation, for so often I find a discrepancy between the expected and the actual date of parturition.

Method of Induction.

I believe that up to 38 weeks' gestation any method of induction to be effective must involve some mechanical intra-uterine procedure. In other words, I do not believe that quinine and castor-oil, with or without pituitary extract, will induce labour until after 38 weeks' gestation. Conversely, I think that if quinine gr. 30 and castor-oil do not initiate labour, the patient is not yet at 38 weeks' gestation—with one exception, that it is possible that uterine inertia may be present.

In cases between 38 to 40 weeks' gestation, therefore, induction of labour can confidently be attempted by the administration of quinine gr. 30 in doses of gr. 10 hourly, preceded by castor-oil 1 ounce, and followed by a simple enema.

This method of induction of labour is frequently used in patients who are nearly at term by size and dates and in whom the blood-pressure is moderately raised and if there is little or no reaction to treatment.

It is sometimes used in cases of so-called post-maturity, which I believe to be extremely rare, and by its use can demonstrate that the calculation of the expected confinement is incorrect, either by dates or by estimation of the size.

I think that the death of the foetus due to quinine poisoning is so rare as to be negligible, believing that frequently an obstetric cause of death can be found to explain it.

Contrary to modern opinion and treatment, I do not believe in using rupture of the membranes, or drainage of the liquor

amnii by Drew Smythe's method as justifiable in cases in which it is hoped to deliver a live child. I still believe in the old teaching of retaining the amnion intact and conserving the liquor amnii if possible, until full dilatation of the cervix, particularly in the primipara.

In the multipara, rupture of the membranes is not so important, since the birth canal (soft parts) is then more pliable and dilates quicker. For the above reason I do not use pituitary extract after quinine, as I think it frequently initiates labour by rupturing the membranes.

Another objection to rupture of the membranes is the introduction of some instruments to effect drainage of the liquor amnii, but this applies equally to the method, which I favour, of introducing a stomach tube or gum elastic bougies into the uterus. I think that a stomach tube is more effective but is more likely to require an anaesthetic, especially in the primigravida, and also the operator needs more skilled assistance than when he uses bougies.

In those cases in which it is realized that the foetus is dead an attempt should be made, and is usually successful, to induce labour by giving stilboestrol. This can be given by mouth, 1 mgm. hourly for 12 doses, followed by quinine if labour does not start.

The whole treatment is repeated again after 24 hours if the first be not effective. If the second trial fails, rupture of the membranes, or the introduction of a tube, will be found to be effective.

Analysis of Cases

During the five years from November, 1932, to November, 1937, there were approximately 14,172 admissions to the maternity clinic in Walton Hospital, and of these, 905 cases of albuminuria were admitted to the antenatal ward for investigation and treatment; i.e. an incidence of 6.3 per cent. During this period there were approximately 11,833 patients delivered, and of these 859 had albuminuria, which is an incidence of deliveries of patients suffering from albuminuria of 7.2 per cent.

This analysis is concerned with the 859 patients, of whom 851 survived and 8 died, which is a 0.95 per cent mortality rate of deliveries of cases of albuminuria and 0.07 per cent mortality rate of all deliveries, and 0.05 per cent of all admissions during this five-year period. (Table III.)

As explained in the section on the classification of cases, an attempt has not been made to divide up this series except to indicate the numbers of cases which were left to nature, 767; the number of patients who were induced, 92, and the number who suffered from eclampsia, 63, which latter includes 7 patients suffering from fits who were delivered at home and were admitted for treatment.

Patients with a previous history of scarlet fever. In 110 cases there was a history of scarlet fever previously; i.e., 12.8 per cent. (Table IV.) More than half these cases occurred in primigravidae, and foetal mortality was just 25 per cent of the live births.

Patients with a previous history suggestive of renal damage, such as eclampsia and albuminuria. In 75 cases there was some history of previous trouble; i.e. 8.7 per cent. (Table V.) In 11 cases there was a history of eclampsia and in 44 there was a history of albuminuria or nephritis, and the foetal mortality rate was practically 50 per cent of the live births.

Symptoms and Signs.

Oedema is both a symptom and a sign. The main complaint of oedema is almost invariably of swelling of the legs and occasionally of hands and face. Oedema may be noted in sites such as the back, abdominal wall, and retina, where it is unnoticed by the patient. It was noted as a symptom or sign associated with albuminuria in 594 cases, i.e. 69.6 per cent, more particularly in the young primigravidae. (Table VI.)

Headaches constitute the next commonest symptom in this series, there being a complaint of headache in 384 cases alone, i.e. 44.7 per cent, and in 129 cases with complaints of alterations in vision, a total of 513 cases, i.e. 60 per cent. (Table VI.)

Eye signs occurred in 182 cases alone and in 129 in association with headaches, a total of 311, i.e. 36.2 per cent. (Table VI.)

Vomiting occurred in frequency in a position intermediate between headache and eye troubles, being a feature in 230 cases, i.e. 26.7 per cent. (Table VII.)

Casts in urine I believe to be an important sign, and in those cases in which casts are constant and in some quantity take their presence to indicate a definite degree of renal damage. Further, the type of cast indicates roughly the degree of involvement. In this series casts were noted in 225 cases, i.e. 26.1 per cent. (Table VII.)

Ambulatory Cases.

It was found that 202 cases, i.e. 23.8 per cent, were able to be discharged during treatment, and were readmitted for their confinements. (Table VIII.) A further number of 44 patients were discharged undelivered, but as they did not return for their deliveries are not included in these results.

As regards the results of confinements of these ambulatory cases, roughly 12 per cent of babies were lost, which is much lower than the total foetal mortality rate. This shows that this is a suitable method for out-patient treatment of slight cases and has not a bad effect on the chances of foetal survival.

The Presence of Signs in the Lying-in Period.

As was stated in the section on classification, the behaviour of the blood-pressure was latterly noted in the lying-in period, i.e. for 10 to 14 days after parturition, and the cases in which records were made have been divided into four groups (Table IX), namely:

1. Blood-pressure in the puerperium higher than on admission.
2. Blood-pressure in the puerperium higher than during treatment.
3. Blood-pressure in the puerperium the same as during treatment.
4. Blood-pressure in the puerperium lower than during treatment.

It will be seen that records are available in 560 cases and that Group 4 contains very many more than any of the others, which is to be expected in those patients in whom there is only a temporary renal damage.

I would regard the cases in Group 3, Group 2, and Group 1 as increasing in severity, and in the seriousness in prognosis both from the point of view of the after-history of the patients and from the aspect of any subsequent pregnancies.

I believe that this would form a good method of classification, particularly from the prognostic point of view. The obvious disadvantage is that such a classification can only be made after parturition and does not give any help during the pregnancy while the patient is under treatment.

Albuminuria Postpartum.

In 225 cases, i.e. 26.1 per cent, there was persistence of

albuminuria during the lying-in period. (Table X.) That this is a sign of severe renal damage is evidenced by the fact that in these cases half the number of babies are lost either as stillbirths or neonatal deaths, and the probable cause, also associated with the condition of renal function, is that more than a third of the number of babies are born prematurely.

Albuminuria persisting in the lying-in period may be considered of serious import, and results are again useful in deciding upon the nature of the renal lesion, whether temporary or permanent, and will be particularly valuable in assessing the prognosis.

Result in Subsequent Pregnancies. (*Table XI.*)

In 152 patients in whom repeated pregnancies and a certain proportion of labours came under notice either by being admitted to the clinic or attending the antenatal clinic, it may be noted that normal pregnancies, i.e. free from albuminuria and symptoms, occurred in more than half the cases, and the known deliveries were practically all alive.

Maternal Mortality.

There were 8 maternal deaths (Table III) due to the following causes: 1 acute atrophy of the liver, 1 accidental haemorrhage, 1 postpartum haemorrhage, 1 uraemic coma, 2 postpartum shock (collision of twins, adherent placenta and manual removal), 2 eclampsia (postpartum, intrapartum).

SHORT NOTES OF CASES OF MATERNAL DEATHS

B.14607. No. 4; A.J.; aged 40; 2-gravida. Her first child was born normally 15 years previously. Last menstrual period end of February, 1932. Expected confinement end of November, 1932.

On November 2nd, 1932, the patient first attended the antenatal clinic showing some oedema and a trace of albumin in the urine, with a history of vomiting for a month. She was admitted to hospital the same day. Blood-pressure 190 systolic; trace of albumin in urine with granular casts, and oedema of ankles. She said that she had had loss of vision in the right eye on two occasions.

November 3rd, 1932, an injection of 10 c.c. magnesium sulphate solution 20 per cent was given. November 25th, 1932, rapid delivery of stillborn female. Shortly afterwards the patient complained of severe epigastric pain, and died. Post-mortem examination not allowed.

C.10073. No. 88: M.J.H.; aged 34; 2-gravida. First child born alive by use of forceps. Left mento posterior; December 1st, 1932. Expected confinement September 8th, 1933.

She first attended the clinic on May 22nd, 1933, when the blood-pressure was 130/100, and her urine free of albumin. Admitted to hospital August 15th, 1933, with burning pain in the epigastrium, and occasional vomiting. Blood-pressure 160/100. Some albumin and blood in the urine. Labour commenced on August 25th, 1933, with bleeding and abdominal pain. Diagnosis of mixed accidental haemorrhage; treated by rupture of membranes. Stillborn male child was born, followed by collapse and death. Post-mortem examination not allowed.

B.10791. No. 146; E.G.; aged 40; 10-gravida. Eight normal labours. Last child stillborn prematurely, followed by manual removal of placenta, and puerperal pyrexia. Last menstrual period July 17th, 1933; expected confinement April 24th, 1934.

The patient was admitted in labour on April 24th, 1934, with breech presentation and extended legs. Albuminuria was present; and she was drowsy. Said that she had not been well, but had not attended any clinic. A stillborn child was delivered on the same day.

On April 26th, 1934, she complained of abdominal pain and pain in the left loin; her temperature was 104°F.; pulse-rate 140; blood-pressure 170/110. April 27th, 1934, rigor in morning; distension of the abdomen; drowsy; lumbar puncture—normal fluid. Stuperose condition, roused with difficulty. The patient died the next day. Post-mortem examination not allowed.

C.10068. No. 399; W.S.; aged 40; 13-gravida. Ten normal confinements with 2 miscarriages. Last child born 16 months previous, when the patient had postpartum haemorrhage.

She attended the antenatal clinic on November 25th, 1935, and complained of heartburn. There was a trace of albumin in urine; blood count 4 million red cells, 10,800 white cells; haemoglobin 42 per cent.

Admitted on January 6th, 1936; blood-pressure 170/114. January 13th, blood-pressure 140/90. A trace of albumin in urine. On January 14th, 1936, the patient was delivered of a hydrocephalic foetus after perforation. Postpartum haemorrhage was severe; she collapsed and died 3 hours later in spite of blood transfusion.

Post-mortem examination showed some fatty degeneration of liver, and slight nephro-sclerosis.

H.6745. No. 509; C.E.; aged 32; 1-gravida. Last menstrual period November 21st, 1935. Expected confinement August 28th, 1936.

She was admitted in labour on July 5th, 1936, with albuminuria; blood-pressure 200/150.

Diagnosis with difficulty of twins. Legs of first child protruding through vulva. Head of second child in pelvis by side of breech. It was impossible to push the legs up past the head of the second child, so the head was perforated and extracted.

The first child was then delivered as a breech. One placenta was

expressed, but the other was retained. The patient collapsed and died in spite of intravenous gum saline. Post-mortem examination was not made.

H.6824. No. 482; C.M.; aged 24; 1-gravida. Last menstrual period end of September, 1935. Expected confinement June, 1936.

On January 6th, 1936, the patient attended the antenatal clinic. She was admitted on June 7th, 1936, for a few days for investigation. Albuminuria. Blood-pressure 120/80.

Labour commenced on July 6th, 1936, and on July 8th a live child was delivered by the low forceps operation. Manual removal of the placenta was carried out; the patient collapsed and died.

Post-mortem examination showed typical focal necrosis areas present in the liver.

K.4374. No. 762; M.E.J.; aged 30 years; 2-gravida. First pregnancy and confinement normal. Last menstrual period, August 21st, 1936; expected confinement May 28th, 1937.

She was admitted on April 24th, 1937, with albuminuria, hyaline and granular casts in the urine; blood-pressure 130/90. Blood count 3,520,000 red cells; 6,500 white cells; haemoglobin 60 per cent. On May 3rd, 1937, there was abdominal pain and vomiting. In labour; fit at the end of the second stage of labour. Child, stillborn, delivered by the forceps. Patient died very soon after.

Post-mortem examination showed focal necrosis in liver. Large cerebral haemorrhage; chronic nephritis.

E.7875. No. 574; A.W., aged 19; 1-gravida. History of oedema of ankles recently. Child born at home. Patient admitted after delivery with postpartum eclampsia.

The patient had status epilepticus, and died in spite of treatment which included intravenous injections of magnesium sulphate, morphia, and lumbar puncture. Her urine contained blood, albumin, and granular casts.

Post-mortem examination showed haemorrhages and areas of focal necrosis in liver. Large basal cerebral haemorrhage.

Foetal Mortality.

In this series there were 113 stillbirths (Table XII) in which number are included 9 abortions, i.e. foetûs of non-viable age, and 44 neonatal deaths (Table XIII), giving a total of 157 or 18.4 per cent of deliveries in this series.

If from the total of stillbirths the cases of death due to foetal deformities and obstetric difficulties and operations be omitted, the corrected number of stillbirths would be 97: Anencephaly 3, general oedema of the foetus 1, microcephaly 1,

hydrocephaly 4, meningocele 1, breech presentation 2, forceps extraction 3, face presentation 1.

Similarly, if from the total of neonatal deaths congenital deformities and diseases and acquired diseases during and after birth causing death be omitted, the number of neonatal deaths would be 37: Diaphragmatic hernia 1, foetal deformities 1, foetal ascites 1, hydrocephalus 2, intracranial haemorrhage 1, haemorrhagic disease of the newborn 2.

The corrected foetal mortality would then be 134, or 15.7 per cent of the total deliveries.

Induction of Abortion or Labour.

In this series of cases induction of abortion or labour was performed in 92 cases, which is 10.8 per cent of the patients delivered. If, however, those patients delivered at term, and induced by quinine (38), be omitted, the induction-rate will be 6.2 per cent.

It will be seen in Table XIV that the majority of inductions at term were effected by quinine; in fact the only induction of premature labour produced by quinine was in the case of twins in a primigravida.

It will be noted that of 94 foetûs born, 56 were born alive and survived, while 38 were lost; 31 being stillborn and 7 dying after delivery.

In this number of inductions is included 6 cases of induction of abortion which are included in the figures of stillbirths.

In Table XV it will be seen that induction of labour was carried out most frequently in primigravidae, and in the third decade of life.

Eclampsia. (*Table XVI.*)

In this series eclamptic convulsions occurred in 63 cases, i.e. 7.3 per cent of the total. The majority of the patients were admitted in a condition of eclampsism, but 24 were already in hospital under treatment when fits commenced, usually in association with labour.

Of the postpartum cases 7 occurred in women who were delivered at home and were transferred after the onset of convulsions. One of these patients had the maximum of fits, 20, seen in any one patient in this series, and who in fact had a condition of status epilepticus, and died with cerebral haemor-

rhage. Another case of postpartum eclampsia occurred in a quartipara, aged 35, 7 days after delivery.

In these patients the time of onset of fits was as follows: Antepartum 20, intrapartum 34, and postpartum 9. The average number of fits per patient was 3.6.

There were two maternal deaths, 3.1 per cent of the total (see Maternal deaths): 1 primipara postpartum and 1 secundipara intrapartum.

In the foetûs delivered 39 were alive, 21 were stillborn, and 4 died; foetal mortality rate, 39.6 per cent. There was one case of twins.

The incidence of eclampsia was greatest in the primigravidae (41 in 63 cases, i.e. 65 per cent) and in the third decade of life. As regards the seasonal incidence, a maximum was reached in the months of March, April, July, August, and October (Table XVII) which suggests that eclampsia occurs fairly equally throughout the year. The cases calculated quarterly, however, show an appreciable rise in the third quarter of the year. First three months, 13; second three months, 15; third three months, 19; fourth three months, 16.

Cases requiring Operative Delivery.

Caesarean section (Table XVIII). Caesarean section was performed on 8 patients in whom some obstetrical abnormality complicated the albuminuric condition. With the exception of one case, that of the 'habitual stillbirth', the lower segment Caesarean section was performed after the onset of labour. The exception was in that of the patient who had had two stillbirths born prematurely. In this case, while the patient was under observation and treatment for albuminuria—which, however, appeared very slight—it was noticed that the foetal heart became very irregular. A hurried classical Caesarean section was performed, and a premature infant, which soon died, delivered. Post-mortem examination revealed the fact that the foetus had a diaphragmatic hernia. (*Note.*—This woman has recently been under our care with her fourth pregnancy since this series, again with a slight albuminuria. Treatment with increasing doses of thyroid extract up to gr. 4 daily carried the pregnancy safely to term and through a normal labour.)

The other case of neonatal death was one of disproportion, in which the foetus was affected by intracranial haemorrhage.

There were no maternal deaths.

In addition to the foregoing Caesarean section, there was a case of abdominal hysterectomy performed on a patient with an immature foetus in order to procure abortion and sterilization of the patient.

Delivery by the forceps (Table XIX). Delivery by the forceps was employed in 35 cases, i.e. in 4 per cent of deliveries, and in 3 cases the child was stillborn, i.e. in 9 per cent. In 8 of these cases in which the foetus survived the patient had eclampsia. There was one maternal death, which followed manual removal of the placenta, and was associated with liver necrosis.

Other Complications of Parturition.

Accidental haemorrhage (Table XX). It is stated that albuminuria predisposes to accidental haemorrhage. In this series there were 20 cases, i.e. 2.3 per cent of cases. In one case, of mixed accidental haemorrhage, treated by rupture of the membranes, the patient collapsed and died soon after delivery. (See Maternal deaths.) Only 3 of the foetûs were born alive, 17 being stillborn. The routine treatment for accidental haemorrhage is morphia gr. $\frac{1}{4}$, artificial rupture of the membranes at the internal os, as tight an abdominal binder as the patient will tolerate, and a whole blood transfusion if necessary.

Placenta praevia (Table XXI). Placenta praevia, which is normally much more common a condition than accidental haemorrhage, occurred only twice in this series, i.e. 0.2 per cent. These patients were treated by the injection of morphia gr. $\frac{1}{4}$ and rupture of the membranes. There were no maternal nor foetal deaths.

Postpartum haemorrhage (Table XXII). In this series there were 15 cases, i.e. 1.7 per cent. There was one maternal death associated with severe haemorrhage. (See Maternal deaths.)

Twins (Table XXIII). There were 25 cases of twins in this series, i.e. 2.9 per cent of cases. In one case the mother died of exhaustion following collision of the twins, and the necessity for perforation of one and later removal of the placenta. (See Maternal deaths.)

Vitamin C.

Towards the end of this series Rotter's skin test for saturation of the body with vitamin C was performed in a small number of patients, viz. 20.

Technique of the test. According to B. Portnoy and F. J.

Wilkinson[5] the test consists in injecting 0.01 c.c. of freshly prepared sterile solution (2 mgm. in 4.9 c.c. water) of 2:6 dichlorphenolindophenol, intradermically, into four adjacent spots in the skin of the front of the forearm, free from veins and hairs, producing four small weals 2 mm. in diameter, and noting the average time of disappearance of the blue colour in the weals. (Table XXIV.)

Patients in whom the blue colour disappeared in 5 minutes were considered to be 'saturated'; 'normal' cases took from 5 to 10 minutes for the colour to disappear; and 'difficult' cases took longer than 10 minutes.

In this series there was one case of eclampsia in which discoloration took 4 minutes, which suggests that it was saturated. The majority of cases, 15, took from 5 to 10 minutes, and are to be considered normal. Only 3 cases took less than 5 minutes and 2 more than 10 minutes to be discolorized, suggesting saturation and deficiency respectively.

In the great majority of cases, therefore, the presence of vitamin C is to be considered normal.

Summary

The treatment of albuminuria of pregnancy as carried out in the obstetric clinic in Walton Hospital, Liverpool, is described.

During a period of 5 years 905 patients suffering from all types of albuminuria except the hyperemesis of early pregnancy were treated, and particulars of 859 patients who were delivered in the clinic are herein collected and tabulated.

In 859 patients there were 8 maternal deaths, with 113 stillbirths and 45 neonatal deaths.

There were 63 cases of eclampsia with 2 maternal deaths.

Induction of abortion or labour was practised on account of symptoms in 92 patients, and abdominal hysterectomy with sterilization in 1 patient.

Caesarean section was performed in 8 cases during labour for some obstetric indication.

Acknowledgments

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TABLE I.

	BREAKFAST, 7 A.M.	10.30 A.M.	LUNCH 1 P.M.	TEA, 4 P.M.	SUPPER, 7 P.M.
Sunday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	Beef, 4 ounces Cabbage, 4 ounces Potatoes, 4 ounces Fruit pudding, 4 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Jelly and custard	Milk, cocoa, or coffee, 5 ounces
Monday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	Meat hash, 4 ounces Carrots and turnips, 4 ounces Potatoes, 4 ounces Fig pudding, 4 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Fish, 4 ounces	Milk, cocoa, or coffee, 5 ounces
Tuesday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	Ox heart and stuffing, 3 ounces Peas, 4 ounces Potatoes, 4 ounces Rice pudding, 6 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Fish, 4 ounces	Milk, cocoa, or coffee, 5 ounces
Wednesday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	Hot-pot, ¾ pound Fig pudding, 4 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Fish, 4 ounces	Milk, cocoa, or coffee, 5 ounces
Thursday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	1 sausage Peas, 4 ounces Potatoes, 4 ounces Rice pudding, 6 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Fish, 4 ounces	Milk, cocoa, or coffee, 5 ounces
Friday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	Steamed fish, 6 ounces Parsley sauce Potatoes, 4 ounces Sponge pudding, 4 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Jam, 1 ounce	Milk, cocoa, or coffee, 5 ounces
Saturday	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Porridge, 6 ounces	Milk or cocoa 5 ounces	Potato pie, ¾ pound Rice pudding, 6 ounces	Tea, 5 ounces Bread, 2 ounces Butter, ¾ ounce Fish, 4 ounces	Milk, cocoa, or coffee, 5 ounces

TABLE II.

WALTON HOSPITAL. MATERNITY DEPARTMENT.

URINE AND BLOOD-PRESSURE CHART.

PREGNANCY — *Date of Admission*

L.M.P.

E.C. — *Date of Discharge*

Name — *Age*

DATE	
Esbach.	B.P.
7	200
6½	190
6	180
5½	170
5	160
4½	150
4	140
3½	130
3	120
2½	110
2	100
1½	90
1	80
¾	70
½	60
¼	50
Trace	40

AMOUNT OF URINE OUTPUT IN 24 HOURS

INTAKE

HEADACHE

OEDEMA

VOMITING

BOWELS

F.H.S.

TABLE III.

PATIENTS DELIVERED, 859.

Age groups	Survived, 851	Died, 8
11 to 20	56	—
21 to 30	473	2
31 to 40	265	5
41 to 50	57	1
	Parity.	
1	366	3
2	148	3
3	89	
4	68	
5	43	
6	31	
7	23	
8	23	
9	15	
10	18	1
11	11	
12	4	
13	4	1
14	3	
15	3	
16	1	
17	—	
18	1	

Table IV.

Cases with Previous History of Scarlet Fever and Results in Present Pregnancy.

110 Cases.

Age groups	
11 to 20	14
21 to 30	55
31 to 40	36
41 to 50	5

Parity.

1	2	3	4	5	6	7	8	9	10	11	12
58	17	8	11	5	2	1	–	4	2	1	1

Foetal results.

Alive	Stillborn	Died
88	16	6

Table V.

Cases with Previous History Suggestive of Toxaemia with Results of Present Pregnancy.

75 Cases.

Age groups	
11 to 20	2
21 to 30	28
31 to 40	39
41 to 50	6

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
5	14	11	8	11	4	5	4	5	4	–	1	1	–	2

Previous eclampsia	Previous albuminuria or nephritis	Previous stillbirths or abortions
11	44	20

Foetal results.

Alive	Stillborn	Died
52	18	5

TABLE VI.

OEDEMA 594 CASES.

Age groups	
11 to 20	41
21 to 30	327
31 to 40	190
41 to 50	36

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18
266	84	61	41	35	24	21	20	11	14	6	4	3	1	2	1

HEADACHE 384 CASES.

Age groups	
11 to 20	25
21 to 30	201
31 to 40	136
41 to 50	22

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18
151	61	37	36	25	18	15	10	8	8	5	3	1	2	3	1

EYE SYMPTOMS 182 CASES.

Age groups	
11 to 20	5
21 to 30	87
31 to 40	80
41 to 50	10

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18
56	29	20	18	19	4	9	8	5	4	3	2	1	1	2	1

TABLE VII.

COMBINED HEADACHE AND EYE SYMPTOMS.
129 CASES.

Age groups	
11 to 20	4
21 to 30	55
31 to 40	64
41 to 50	6

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18
38	18	13	13	16	4	7	5	3	3	3	1	1	1	2	1

VOMITING 230 CASES.

Age groups	
11 to 20	14
21 to 30	128
31 to 40	79
41 to 50	9

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
101	43	28	13	12	5	6	7	4	5	1	1	1	1	2	—

CASTS IN URINE 225 CASES.

Age groups	
11 to 20	12
21 to 30	132
31 to 40	63
41 to 50	18

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
110	38	21	15	15	5	6	6	3	2	1	—	2	1	—	—

TABLE VIII.

PATIENTS DISCHARGED AFTER INVESTIGATION AND TREATMENT, AND RE-ADMITTED FOR DELIVERY (202 CASES).

Age groups	
11 to 20	13
21 to 30	122
31 to 40	60
41 to 50	7

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14
79	47	22	18	8	7	6	5	2	3	3	2	—	—

Foetal results.

Alive	Stillborn	Died
177	17	8

TABLE IX.

Blood-pressure in puerperium higher than on admission (40 cases).

Age groups	
11 to 20	3
21 to 30	17
31 to 40	15
41 to 50	5

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
15	5	5	5	2	3	—	—	1	2	1	—	—	1	—	—

Blood-pressure in puerperium higher than during treatment (74 cases).

Age groups	
11 to 20	6
21 to 30	33
31 to 40	31
41 to 50	4

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	20	10	5	3	3	2	—	3	2	1	—	—	—	—	—

Blood-pressure in puerperium same as during treatment (52 cases).

Age groups	
11 to 20	3
21 to 30	30
31 to 40	15
41 to 50	5

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
24	9	3	6	1	4	1	2	1	1	—	—	—	1	—	—

Blood-pressure in puerperium lower than during treatment (394 cases).

Age groups	
11 to 20	24
21 to 30	288
31 to 40	110
41 to 50	31

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
184	53	35	28	30	13	9	15	6	5	8	2	1	1	2	1

TABLE X.

CASES WITH ALBUMINURIA POSTPARTUM (225 CASES).

Age groups	
11 to 20	15
21 to 30	125
31 to 40	71
41 to 50	14

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
109	35	22	15	15	8	4	2	3	4	3	1	2	1	1

Foetal results.

Alive	Stillborn	Died	Premature	Term
170	41	14	66	159

TABLE XI.

RESULTS IN SUBSEQUENT PREGNANCIES (152 CASES).

Age groups	
11 to 20	6
21 to 30	91
31 to 40	47
41 to 50	8

Parity.

1	2	3	4	5	6	7	8	9	10	11
82	29	10	9	5	3	6	1	2	4	1

Pregnancy.

Normal	Abnormal
88	64

Foetal results.

Alive	Stillborn	Died	Unknown
118	6	2	30

TABLE XII.

STILLBIRTHS (113 CASES).

Acute liver atrophy	1	General oedema	1
Anencephaly	3	Microcephalic foetus	1
Accidental haemorrhage	16	Hydrocephalic foetus	4
Eclampsia	20	Twins	5
Macerated, 29		Breech presentation	2
Premature	26	Face presentation	1
Term	3	Delivery by the forceps	3
Abortion, 9		Meningocele	1
Induction	7	Hysterotomy	1
Spontaneous	2	Quinine induction	3
Prematurity, 10		Unknown	3
Induced	6		
Spontaneous	4		

TABLE XIII.

NEONATAL DEATHS (45 CASES).

Prematurity, 23		Twins: One	2
Spontaneous	15	Both	4
Induced	8	Hydrocephalus	2
Diaphragmatic hernia and prematurity	1	Foetal ascites	1
Eclampsia	3	Foetal deformities	1
Syphilis	1	Haemorrhagic disease	2
		Intracranial haemorrhage	1
		Unknown	4

TABLE XIV.

INDUCTION OF LABOUR (92 CASES).

Age groups

11 to 20	5
21 to 30	47
31 to 40	29
41 to 50	11

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
41	15	7	5	5	5	1	2	4	3	1	—	1	1	1

Methods of Induction.

	Stomach tube	Rupture of membranes	Quinine	Quinine and oestrin
Term	7	2	37	—
Premature ...	33	10	1	2

Foetal results.

	Alive	Stillborn		
		Fresh	Macerated	Died
Term	38	5	—	1
Premature ...	18	15	11	6

TABLE XV.

ABORTIONS (14 CASES).

Spontaneous (8 Cases).

Age groups

21 to 30	5
31 to 40	3

Parity.

1	2	3	4	5	6	7	8	9	10	11
4	1	1	—	—	—	1	—	—	—	1

Induced (6 Cases).

Age groups

21 to 30	1
31 to 40	3
41 to 50	2

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
—	3	—	1	—	1	—	—	—	—	—	—	—	—	1

TABLE XVI.

ECLAMPSIA (63 CASES).

Age groups

11 to 20	5
21 to 30	43*
31 to 40	13*
41 to 50	2

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
41*	7*	3	1	6	2	1	2	—	—	—	—	—	—	—	—

* One died.

Antepartum	Intrapartum	Postpartum
20	34	9

Foetal results.

Alive	Stillborn	Died
38	21	4

Seasonal incidence of Quarters

First three months	13
Second three months	15
Third three months	19
Fourth three months	16

Monthly Incidence.

J	F	M	A	M	J	J	A	S	O	N	D
2	4	7	7	5	3	7	7	5	7	5	4

TABLE XVII.

GRAPH OF INCIDENCE.

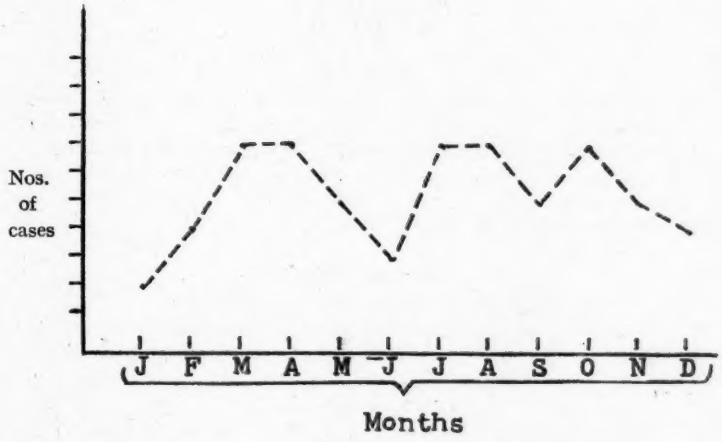

TABLE XVIII.

CAESAREAN SECTION (8 CASES).

Age groups	
21 to 30	4
31 to 40	1
41 to 50	3 of which 2 were in 1 case

Parity.

1	2	3	4	5	6	7
4	2	1	—	1	—	—

Indications.

Breech with extended legs	Disproportion	Rigid cervix	Habitual stillborn
1 (1 with presentation of cord)	4	1	1

Foetal results.

Alive	Stillborn	Died
6 (2 in 1 case)	—	2

One case of Abdominal Hysterotomy with Sterilization.

Age group	Parity						
	1	2	3	4	5	6	7
21 to 30	—	—	—	—	1	—	—

Stillborn
1

TABLE XIX.

FORCEPS DELIVERY (35 CASES).

Age groups	
11 to 20	3
21 to 30	24*
31 to 40	6
41 to 50	2

* One died.

Parity.

1	2	3	4	5	6	7	8
30*	4	—	—	—	—	—	1

* 8 in eclampsia.

Foetal results.

Alive	Stillborn	Died
32 (8 in eclampsia)	3	—

TABLE XX.

ACCIDENTAL HAEMORRHAGE (20 CASES).

Age groups	
11 to 20	1
21 to 30	9
31 to 40	8*
41 to 50	2

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
6	2*	4	1	4	1	—	—	—	—	1	—	1	—	—

* One died.

Foetal results.

Alive	Stillborn	Died
3	17	—

TABLE XXI.

PLACENTA PRAEVIA (2 CASES).

Age groups	
21 to 30	1
31 to 40	1

Parity.

1	2	3	4	5	6	7	8	9	10
—	1	—	—	—	—	—	—	—	1

Foetal results.

Alive	Stillborn	Died
2	—	—

TABLE XXII.

POSTPARTUM HAEMORRHAGE (15 CASES).

Age groups	
11 to 20	1
21 to 30	10
31 to 40	4*
41 to 50	—

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13
8	1	4	—	—	1	—	—	—	—	—	—	1*

* One died.

Foetal results.

Alive	Stillborn	Died
14	1	—

TABLE XXIII.

TWINS (25 CASES).

Age groups	
11 to 20	1
21 to 30	11
31 to 40	11*
41 to 50	2

Parity.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
10*	3	4	2	2	—	1	1	1	—	1	—	—	—	—

* One died.

Foetal results.

Both survived	17
Both died	2
One survived	
One stillborn	4
One died	
One stillborn	1
One alive	
One died	1

TABLE XXIV.

VITAMIN C CONTENT (20 CASES).

Age groups	
11 to 20	2
21 to 30	11
31 to 40	4
41 to 50	3

Parity.

1	2	3	4	5	6	7	8	9	10	11
7	4	2	2	—	1	1	2	—	—	1

Results of foetus.

Alive	Stillborn	Died
17	3	1

Times of discoloration.

Minutes

1	2	3	4	5	6	7	8	9	10	11	12	13
—	—	1	2	4	1	2	1	3	4	1	—	1

Ocular Complications in Hyperemesis Gravidarum

BY

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ALTHOUGH the so-called retinitis of pregnancy has long been recognized as a grave complication, and one justifying or demanding the premature termination of pregnancy, the ocular disturbances which may accompany pernicious vomiting in the earlier months are much less widely known and receive comparatively little notice in the textbooks of obstetrics and none at all, so far as one can discover, in those of ophthalmology. Nevertheless several papers on the subject have been published within recent years, chiefly in the United States, the findings of which deserve to be more generally known.

It is difficult to assess the importance of this matter to obstetric practice in general. In the first place, estimates of the frequency of pernicious vomiting in pregnancy vary a good deal, and perhaps the incidence of hyperemesis gravidarum varies from one locality to another. The annual reports of the Glasgow Royal Maternity and Women's Hospital for the five years 1934 to 1938 show that, on an average, 90 patients suffering from persistent vomiting (10 to 23 of the cases described as very severe) were admitted annually for in-patient treatment, while the corresponding figure for the Edinburgh Royal Infirmary was 59 cases per annum (Fahmy,[1] 1940).

The importance of hyperemesis gravidarum as a cause of maternal mortality is indicated by the fact that of the 449 patients admitted to the Glasgow Maternity Hospital on account of hyperemesis, both moderate and severe, 3.5 per cent died, while of the 295 patients admitted to the Edinburgh Royal Infirmary during the same period, 3.7 per cent died. The Glasgow figures represent some 4.4 per cent of the total maternal deaths in the hospital, substantially the same as the rate given in the 1935 report of the Department of Health for Scotland on Maternal Mortality in the period 1929 to 1933.

As regards the ocular complications, there must be many

obstetricians who have no personal experience of these, if one may judge by the scanty references to the subject in modern obstetrical literature. Several standard textbooks published within the last three years have no reference to the subject and others merely refer to the fact that retinal haemorrhages may be discovered in the more serious cases.

Aetiology

The character of the ocular disturbances, which will be described, has an important bearing on the aetiology of persistent vomiting, as to which there is still no general agreement. The fact that in many cases, especially of the less pernicious types, there is a strong neurotic element, has led to the view that there are two main groups of cases, the neurotic and the toxic. Different authorities place the emphasis on one or other of these, some holding that every case rests upon a toxaemic basis, while others believe that pernicious toxic vomiting is rare.

Belief in the existence of a neurotic type receives support from the fact that of the patients suffering from persistent vomiting admitted to hospital for treatment by isolation, rest, and dieting, few progress to the pernicious stage. At the same time it is worth noting that among the grave cases admitted to hospital a certain number of the patients had already been in-patients on account of hyperemesis at an earlier period of their pregnancy and had been dismissed, apparently cured, after a short course of treatment. Such an experience tends to break down any apparent distinction between the true neurotic and the other types; indeed, to cast doubt on the existence of a purely neurotic group. The discovery in any case of a central scotoma in the field of vision, even without changes in the fundi, definitely puts neurosis out of court.

Endocrine disturbances, focal infections, and glycogen depletion are among suggested causes; but within the last 3 or 4 years there has been a growing belief that deficiency of vitamin B_1 is an important factor in bringing about the complications of hyperemesis gravidarum.

Polyneuritis as well as optic neuritis may complicate these cases, and on the analogy of beri-beri (in which optic neuritis has been reported) a vitamin B_1 deficiency seems a reasonable assumption. Support for this view is afforded by the occurrence of optic neuritis in the persistent vomiting following certain surgical operations (Wagener and Weir,[2] 1937).

Winans and Perry[3] (1936) report good results from the administration of vitamin B_1 in the polyneuritis accompanying persistent vomiting in pregnancy. Wagener and Weir claim success from vitamin B treatment in one case in which retinal haemorrhages cleared up in about a week. A similar happy result was obtained in the first patient described below, who received a thorough course of vitamin therapy, while her fellow-patient, whose condition, general and ocular, seemed to be no more severe, but who did not have the benefit of the vitamin treatment, died.

It cannot be claimed that these cases settle the question as to the toxic or other cause of hyperemesis gravidarum and its ocular complications. A combination of toxaemia and avitaminosis is, of course, not impossible. Wagener and Weir suppose that both in the persistent vomiting of pregnancy and in that following surgical operations, the lack of vitamin B_1 is brought about by the destruction or removal of the available vitamin in the ingested food. This does not exclude the possibility of a primary toxic cause, any more than one can deny the possibility of a toxic cause for the persistent vomiting or even for the morning sickness of pregnancy.

The Ocular Complications

The disease has usually reached a fairly advanced stage before the patient complains of a pronounced loss of vision, when ophthalmoscopic examination reveals the condition variously described as 'retinal haemorrhage,' 'haemorrhagic retinitis', or 'toxic retinitis'. It is perhaps not surprising that a patient in the throes of a severe hyperemesis, possibly associated with cerebral disturbances, is incapable of recognizing anything short of complete, or at least rapidly advancing, blindness; but it is most desirable that the onset of ocular complications should be recognized at a much earlier stage. One of the principal objects of this paper is to suggest that this is possible.

If the ocular involvement is only discovered when there are profound loss of vision and gross ophthalmoscopic signs, the ophthalmologist can be of little assistance, for the patient is then gravely ill, and obstetricians agree that the termination of pregnancy at this stage adds little to the chances of saving the life of mother or child; indeed, surgical interference may hasten a fatal termination.

According to Schjött-Rivers[4] (1938), the first case of

hyperemesis with impaired vision in which the ophthalmoscope revealed changes in the fundus oculi was that reported by Erisman (1890)—a fatal case which had shown retinal haemorrhages in both eyes. Among the earlier references to the ocular complications is the paper of Stander[5] (1932) who describes two cases of haemorrhagic retinitis in the vomiting of pregnancy. The early and late phases of the fundus picture in one case are well illustrated in a colour plate. Stander expresses the view that the neurotic element in this disease has been greatly overemphasized, and that all cases are toxaemic, though neurosis may play a part of varying significance. In his first case blurring of vision was noticed 9 days after admission on account of uncontrollable vomiting during the 5th month of pregnancy. The discs were found to be normal but surrounded by large retinal and subhyaloid haemorrhages. Routine treatment was unavailing, and the patient died the day following termination of the pregnancy. His second case gave a similar history, but pregnancy was terminated at an earlier stage, and the patient made a slow recovery. The fundus drawings from this case show large haemorrhages radiating from the disc into the adjacent retina. There are no exudates or vascular changes.

Stander's article was closely followed by that of Berkwitz and Lufkin[6] (1932) on the toxic neuronitis of pregnancy. The term 'neuronitis' was introduced instead of neuritis or polyneuritis on the ground that nerve cells as well as peripheral nerves are involved. Forty-eight cases are collected from the literature and the authors add 4 of their own. In their 4 cases, optic neuritis was present as well as the general nervous disturbance. Mental symptoms of a delirious or confusional nature were found in two-thirds of the cases. Berkwitz and Lufkin admit that both the neuronitis and the optic neuritis are rare occurrences, but insist on their importance as an indication for the interruption of pregnancy. They estimate the mortality in these cases as high as 25 per cent.

Tillman[7] (1934), in an account of 2 fatal cases, gives a description of the fundus changes which includes both optic neuritis and haemorrhage; and it is worth noting that at the first examination after the onset of dimness of vision the fundi were normal; 2 days later there was blurring of the discs, and haemorrhages only appeared after a definite papilloedema had established itself. Unfortunately, details of the visual acuity and field of vision are not given; but it is probable that at the date of the first, negative, ophthalmoscopic examination, the dimness

of vision was due to a central scotoma. At the post-mortem examinations in both cases petechial haemorrhages were found in the brain and elsewhere.

To these references should be added the important monograph of Schjött-Rivers. It covers a study of hyperemesis gravidarum in all its aspects, including its biochemistry, and in the chapter on the ocular complications discusses 21 cases from the literature to which the author adds 7 of his own. Attention is called to the severity of the visual loss; its sudden onset and rapid development. He also notes the characteristic situation of the haemorrhages on or adjacent to the disc, the frequent occurrence of papilloedema, and the absence of exudates. The loss of vision being out of all proportion to the fundus changes, he infers that the cause is a retrobulbar neuritis.

Pathology

Sheehan,[9] reviewing the pathology of 19 cases of hyperemesis gravidarum which came to post-mortem examination in the Glasgow Royal Maternity and Women's Hospital, records fatty changes in the liver and kidneys, but lays particular stress upon the occurrence of small haemorrhages in the brain, chiefly in the corpora mamillaria and floor of the fourth ventricle. Similar haemorrhages occurred under the endocardium in four cases. The cerebral haemorrhages, similar to those associated with Wernicke's encephalopathy, had already been recorded by Campbell and Biggart[8] (1939). Several authors have suggested that the haemorrhages are the result of increased permeability of the capillaries, occasioned by some form of toxaemia. The centrilobular necrosis in the liver described by some observers was not found in Sheehan's cases, probably because in his material examination was always made within a very few hours of death. The bibliography given by Sheehan in this paper shows that a great deal of work has been devoted to the pathological aspects of hyperemesis gravidarum, but neither pathology nor biochemistry has determined the part played by toxins, vitamin deficiency, and other factors in the causation of this disorder.

Little is known of the histopathology of the ocular changes. The only reference I have been able to find is to one of Schjött-Rivers's personal cases in which microscopic examination of a section of the optic nerve and papilla did not reveal any signs of inflammation or other changes, although ophthalmoscopic

examination during life had shown papilloedema and some haemorrhages in the neighbourhood of the disc.

Treatment

A detailed discussion of the treatment of hyperemesis gravidarum would be out of place in this communication; but with reference to the cases to be described it may be said that the treatment employed in the Glasgow Royal Maternity and Women's Hospital follows the usual lines, the objectives being removal from disturbing psychological influences, the cure of constipation, the restoration of fluid loss, the correction of acidosis, sedative treatment, and the restoration of food-loss by a nourishing diet as soon as possible. In addition, the administration of vitamins has become a routine procedure.

The practice in regard to therapeutic abortion has varied, but the tendency to-day is to interfere promptly, at an earlier stage, in those patients who do not respond quickly to the more simple treatment.

It is admitted that of the patients admitted to hospital on account of hyperemesis gravidarum and submitted to the simple forms of routine treatment, a large number recover and go on to term without further trouble; but the exceptions are important. In the first place, a certain proportion of the cases thus relieved return after a short interval with a recurrence of vomiting, and the hoped-for response to treatment does not materialize. In the second place, in a high proportion of the fatal cases, vomiting has ceased and food has been retained for several days before death, the end sometimes coming rapidly at a time when improvement seems to have set in. Such a deceptive appearance of recovery adds to the difficulty in deciding for or against surgical treatment. This question is answered, pessimistically, in many standard textbooks by a statement that by the time the patient is so ill as to suggest the surgical interruption of pregnancy, it is too late to save the patient.

It is easy to understand the reluctance of the obstetrician to terminate pregnancy, especially in view of the misleading signs of improvement to which I have just referred. It seems to be beyond doubt that earlier recourse to therapeutic abortion has reduced the percentage of fatal cases, and it is unwise to hesitate in applying surgical treatment when the case assumes a serious aspect. Berkwitz and Lufkin advocate interruption of pregnancy as soon as definite neurological symptoms appear. The

appearance of retinal haemorrhages is universally recognized as a grave sign and is stated to be an indication for termination of pregnancy by Stander, Tillman, Kehrer[10] (1938), Fitzgerald and Webster[11] (1938), and others; but there is no doubt that the percentage of fatalities at this stage is high, and it would be a great boon if some non-surgical form of treatment, applicable at an earlier stage, could be relied upon to ensure more favourable returns. Fortunately there are grounds for believing that vitamin treatment meets this need.

Some of the evidence bearing on the value of vitamin B_1 treatment has already been indicated in reference to the aetiology of hyperemesis gravidarum, and this is sufficient to justify an extended trial of the treatment. If the good results claimed for vitamin treatment are confirmed by further experience, the outlook in this serious condition will be much more hopeful than one would gather from current writings. Even in cases in which vitamin B_1 is not in itself sufficient to effect a cure it is probable that an intensive course of the treatment will greatly improve the outlook for subsequent surgical intervention.

The fact that retinal haemorrhages and petechial haemorrhages in the cerebrum are characteristic of the later phase of the severe cases of hyperemesis gravidarum suggests that there may be an increased permeability of the capillary vessels, and this justifies the addition of vitamin C in the form of redoxon in the Maternity Hospital scheme of treatment.

It is very unlikely that oral administration of the vitamins would have any value at the period when vomiting is still active, but when food is retained and the patient is convalescent, continued oral medication will probably be useful.

The present communication was prompted by the simultaneous occurrence of two striking examples of pernicious vomiting with ocular complications in the antenatal service of the Glasgow Royal Maternity and Women's Hospital. The following is an abstract of the clinical notes:

CASE 1.

Mrs. B., aged 29 years. Two previous pregnancies with hyperemesis in both, but spontaneous deliveries at term. Sickness throughout present pregnancy, mild at first, but increasing till severe and constant. Admitted in 2nd month. Constipated. Blood-pressure, 90/70. Acetone breath. Acetone but no albumin in urine. Retroverted gravid uterus corrected on admission. Discharged well, after 2 weeks of simple routine treatment. Readmitted 5 weeks later, August 2nd, 1940, with history of progressively increasing sickness and vomiting since dismissal. Con-

stipated; blood-pressure, 100/70; toxic; dehydrated; very ill. Treatment as before with addition of intravenous glucose in saline, and intramuscular betaxan, 1 c.c. daily. Thirteen days after readmission complained of dimness of vision. Could not count fingers at 3 feet. Four days later, R.V. = fingers; L.V. = hand movements; and after 2 days, August 21st, 1940, no light perception, even with flash lamp.

At the onset of visual disturbance the house surgeon found retinal haemorrhages. At my first examination on August 19th, 1940, both fundi showed papilloedema, and large haemorrhages radiating from the discs, some from the margin, some from the centre. Other detached haemorrhages; but all near the disc or macula. Retinal exudates were absent. Vessels all full and bright, but arterio-venous ratio unaltered, and evidence of changes in the vessel walls was absent. Neurological examination, negative. Cerebro-spinal fluid was normal, and at normal pressure. On August 21st, 1940, delivery by abdominal hysterotomy under spinal anaesthesia. On the following day vision returning and progressive daily improvement. On August 30th, 1940, R.V. and L.V. = 6/12; September 19th, 1940, R.V. = 6/12, L.V. = 6/6. Full fields. A few haemorrhages in R; no haemorrhages in L.

Two days after operation vitamin C in form of redoxon 4 c.c. daily, intramuscularly, was added, and a few days later vitamins B and C given by the mouth only. When discharged on September 24th, 1940, walking was unsteady, and the power of the limbs somewhat feeble.

Subsequent examination in the eye department of the Western Infirmary gave R.V. = 6/6 partly and Jaeger 2; L.V. = 6/6 partly and Jaeger 2. Fields of vision of normal extent. Central scotoma was absent. Some enlargement of the blind spot. Pupil reactions and ocular movements normal. Ptosis, lagophthalmos and nystagmus were absent. Graefe's sign well marked. Discs pale but free from oedema. Some bleaching of the fundus bordering the discs. Retinal vessels normal. Surface reflexes of the retinae suggested some residual oedema around the maculae. One small punctate haemorrhage in right retina.

A careful neurological examination by Dr. J. Gaylor gave evidence of a peripheral neuritis with possibly some involvement of the cord. Wassermann's reaction in the cerebro-spinal fluid was negative. There were superimposed functional symptoms, and cerebration was somewhat unsatisfactory. It was noteworthy that at the height of her illness her blindness did not seem to concern her.

CASE 2.

Mrs. McC., aged 21, primiparae; admitted August 13th, 1940, in the 12th week of pregnancy. Vomiting throughout pregnancy of increasing severity. Without solid food for 3 weeks before admission. Emaciated; constipated; dehydrated. Urine: Specific gravity 1036, acetone. Traces of albumin and sugar. Blood-pressure, 120/85. Nervous system, etc., normal. General treatment as in Case 1. Vomiting ceased on admission and did not recur, but 11 days after admission complained of rapid loss of vision,

and was found to have bare light perception. Ophthalmoscopic examination on that day, August 24th, 1940, found a picture almost identical with that in Case 1. On the following day abdominal hysterotomy under spinal anaesthesia, but her condition rapidly deteriorated and she died on August 27th, 1940. In this case vitamin B_1 had not been employed but redoxon 4 c.c. intravenously was begun 3 days before death. Post-mortem examination showed, among other things, haemorrhages in inferior corpora quadrigemina, corpora mamillaria, floor of 4th ventricle and walls of 3rd ventricle.

The following are short notes regarding 2 further cases seen some years ago in the Maternity Hospital:

CASE 3.

Mrs. R., aged 26. Admitted May 1st, 1927, in 3rd or 4th month of 2nd pregnancy, on account of hyperemesis. Urine: diacetic acid, acetone, albumin. Catarrh of frontal and ethmoid sinuses. Cerebro-spinal fluid, normal. Sickness ceased on admission, but 3 days later the patient complained of great dimness of vision. A large, dense, central scotoma in the fields of vision reduced vision to " fingers," in the peripheral field. Ophthalmoscopic examination, some oedema of both discs extending into adjacent retina. Temporal segment of both discs pale. Diagnosis was acute retrobulbar neuritis. In 3 days vision failed completely, with increasing blurring and swelling of the discs and one or two haemorrhages. A fortnight after admission there was still no perception of light, although the visible neuritis seemed to be less pronounced. Died 15 days after admission.

CASE 4.

Mrs. L., aged 44; 12th pregnancy. Had been admitted at an earlier period of pregnancy on account of hyperemesis. Dismissed well, but relapsed a week after returning home, and was readmitted on October 31st, 1928. Jaundice. Urine: cells, casts, staphylococcus albus in culture. On admission she complained of dimness of vision. V.A. right eye = " fingers " but a good field. V.A. left eye = light perception. Ophthalmoscopic examination, moderate papilloedema. Haemorrhages or exudates were absent.

I am indebted to my colleague Dr. John Marshall for permission to refer to 2 less advanced cases which have recently been under his notice:

CASE 5.

This was a young woman in her second pregnancy, the first not having gone to term. Hyperemesis had continued for some weeks in spite of treatment. At a first examination her mental state suggested encephalitis lethargica. Visual acuity was markedly reduced, and bedside scotometry elicited a central scotoma. There was some blurring of the

disc margins. Termination of pregnancy was urged, but was not carried out for some days. Her condition became worse and she died.

CASE 6.

The patient was an emaciated woman in her early twenties. At an examination of her eyes 18 months before the occurrence of hyperemesis the only defect discovered was a small amount of hypermetropic astigmatism. Hyperemesis became so persistent that she was removed to hospital. Visual acuity was found to be markedly depressed, and there was a central scotoma. Recovery after the uterus had been emptied was rapid but not complete. Re-examination 6 months later found a very small paracentral scotoma. Visual acuity was 6/9 (slowly). Lateral nystagmus was now noted, which had not been present at the previous examination.

COMMENT

The above 6 cases form an interesting series illustrating the clinical and pathological features referred to in previous publications.

In the first place they make it clear that the description of the ocular complications in hyperemesis gravidarum as retinal haemorrhages, haemorrhagic retinitis, or toxic retinitis is incomplete and misleading. If we consider these cases in series we obtain a much more correct picture of the ocular complications.

The value of Marshall's cases (Cases 5 and 6) lies in the fact that they show that the primary ocular disturbance, a retrobulbar neuritis, can be recognized at an early stage, when there is dimness of vision without visible changes in the fundi. Case 3 carries the matter a stage further, for at the first examination there was considerable dimness of vision, due to a large, dense central scotoma and some oedema of the discs, making possible the diagnosis of retrobulbar neuritis, while haemorrhages developed still later along with increasing optic neuritis and complete loss of vision. The second case in Tillman's communication was very similar—in the first place, dimness of vision with negative ophthalmoscopic examination, later oedema of the discs, and subsequently retinal haemorrhages with more pronounced intraocular neuritis. Cases 1 and 2 were first seen with a fully developed fundus picture of papilloedema, gross retinal haemorrhages and complete blindness. It was not possible at this stage to speak of a retrobulbar neuritis, but the profound loss of vision which could not be accounted for by the haemorrhages or the oedema of the nerve head showed that we were

dealing with an optic neuritis, while the recovery of peripheral vision in advance of central vision suggested that the initial defect would be a central scotoma.

The final condition of the fundi forms a characteristic and unique picture. Along with a well-marked papilloedema we have broad flame-shaped or comet-shaped haemorrhages radiating from the centre or margins of the disc, with perhaps a few discrete haemorrhages near the disc. Exudates do not occur, and the vessels do not show any sclerosis or other organic change. The papilloedema and haemorrhages remind one to some extent of those encountered in subarachnoid haemorrhage, but the cerebro-spinal fluid is normal. In the character of the haemorrhages and in the absence of exudates and vascular changes, the picture differs completely from that seen in diabetes, nephritis, and hyperpiesis. The profound loss of vision excludes these conditions, as well as those characterized by elevation of intracranial pressure.

The association of the ocular signs with those of 'neuronitis' is seen in Case 1, and the paresis of the external rectus muscle in one of Wagener's and Weir's cases was, no doubt, a manifestation of peripheral neuritis; but the optic nerve is not a peripheral nerve; it is part of the brain, and the optic neuritis is probably more closely related to the condition of the brain than to that of the peripheral nerves. Involvement of the brain is indicated by the mental disturbances, lethargy, and so on, in some of the cases, as well as by the haemorrhagic lesions found post-mortem.

Those textbooks which make any reference to the ocular complications of hyperemesis gravidarum agree in stating that the occurrence of retinal haemorrhages is a very grave sign, and an indication for termination of the pregnancy, at the same time pointing out that when this stage is reached the benefit of operation is problematical. In the light of the knowledge derived from these cases, it seems to be incumbent on those authorities to point out that the warning signal is not the gross fundus changes seen when the patient is almost *in extremis*, but a certain mistiness or dimness of vision due to a central defect in the field of vision, and unaccompanied at first by any ophthalmoscopic changes. This dimness may not be impressive, although in acute cases the visual loss may be rapid and profound. In any case, it may easily be overlooked or considered unimportant by both the patient and the obstetrician when the sickness and depression are more urgent.

It would perhaps be a counsel of perfection to suggest that a visual test and ophthalmoscopic examination should be made as much a matter of routine during pregnancy as the examination of urine and blood-pressure; but it is at least possible, and it is certainly desirable, that every complaint of visual disturbance, especially in association with hyperemesis gravidarum, should be investigated. Such an investigation would naturally distinguish the retrobulbar neuritis here referred to from other possible causes of defective vision, of which there are many.

The obstetrician himself may not feel qualified to make the diagnosis of retrobulbar neuritis, but it is just at this stage that the recognition of the defect can be of value, for the discovery of a central scotoma naturally puts the diagnosis of neurotic vomiting out of court, and may lead to the early institution of curative treatment. In this the intensive use of vitamins B_1 and C may play an important part. A comparison of Cases 1 and 2 supports this view.

It is gratifying to find, as we did in Case 1, that when recovery occurs, there may be almost complete restoration of vision, even when light perception has been abolished.

Summary and Conclusions

A short survey is given of the incidence, aetiology, pathology, and treatment of hyperemesis gravidarum.

Doubt is expressed regarding the occurrence of purely neurotic cases, and some support is given to the view that a deficiency of vitamin B_1 and perhaps of vitamin C is an important factor in aetiology.

It is shown that the current description of the ocular complications as haemorrhage and optic neuritis appearing along with a notable loss of vision when the patient is gravely ill, is incomplete and misleading. The earliest ocular disturbance is a retrobulbar optic neuritis associated with a central defect in the field and without visible ophthalmoscopic changes. This is succeeded by a visible oedema of the optic nerve and later by a characteristic type of peripapillary retinal haemorrhage. The ultimate visual defect may amount to total or almost total blindness, which, however, is capable of complete recovery.

The profound visual loss and the form and situation of the haemorrhage, along with the absence of exudates and vessel changes, are important points in the differential diagnosis from the ocular signs of cerebral tumour, subarachnoid haemorrhage,

diabetes, and hyperpiesis. The optic nerve and retina being essentially part of the brain, the optic neuritis and retinal haemorrhages are more closely related to the cerebral complications of hyperemesis gravidarum than to the associated peripheral neuritis.

It is recommended that, in the treatment of persistent vomiting in pregnancy, the routine methods of rest, restoration of fluid loss and correction of constipation should be supplemented by intramuscular administration of vitamins B_1 and C. If these do not give a rapid response, and especially if polyneuritis, retrobulbar neuritis, papilloedema or retinal haemorrhages occur, prompt termination of pregnancy seems to be called for. The cessation of vomiting may be deceptive, and should not in itself be accepted as a sign of recovery without consideration of the patient's general state and the condition of the vision and fundi.

The serious significance of ocular signs should be recognized before the appearance of changes in the retina and optic nerve. By the time that retinal haemorrhages and optic neuritis have become manifest the patient's life is in jeopardy and treatment may be quite ineffective.

A description is given of 6 cases of hyperemesis gravidarum with ocular complications of varying degrees of severity, ranging from slight dimness of vision without ophthalmoscopic changes to total blindness with gross haemorrhages and optic neuritis, and it is recommended that even if an examination of the eyes cannot be carried out periodically in every case of pregnancy, any complaint of defective vision should lead to a careful investigation of the visual acuity and field of vision as well as of the fundi. Early diagnosis of the ocular complications in hyperemesis gravidarum will help to reduce the frequency of one cause of maternal mortality.

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Gynaecological and Puerperal Thrombophlebitis contrasted with Phlegmasia Alba Dolens

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THESE two diseases, so different in their ultimate outcome and yet so similar clinically in their incipient stages, are seldom differentiated, and consequently are seldom rationally treated. The two diseases may be found in post-operative gynaecological cases but more frequently in puerperal infected states. The treatment is so different in the two diseases that it behoves us to arrive at a correct diagnosis as early as possible. This is possible in the vast majority of cases, and when the diagnosis is established the complications which may arise out of each are well known and, therefore, can be anticipated and, in many cases, prevented.

THROMBOPHLEBITIS

Thrombophlebitis may occur following any infection, whether gynaecological or puerperal. I am decidedly of the opinion that thrombophlebitis cannot occur without infection. The infective agent may be very mild and attenuated, and may be devoid of any systemic reaction, such as temperature or elevation of pulse-rate, but the absence of these is no criterion for assuming that infection is not present. Thrombophlebitis, as the compound term implies, is an infection of a vein wall and of its clot. It should be clearly understood that these two factors, phlebitis and thrombus, may differ quantitatively in any two cases in the widest limits of the imagination. In cases of acute infection the phlebitic element usually predominates, with a minimum of thrombus over the intima of the affected vessel or vessels. Whereas, in low-grade infections usually without systemic reactions, the thrombosis may be out of all proportion to the phlebitis. Between these two extremes all variations are found. Thrombophlebitis is much more common than any of us assume because so many of the cases are clinically silent, and make known their occult presence only when

some complication arises out of it. It is a condition that has its origin, in the vast majority of cases, from a diseased, traumatized mucous membrane. The cases of dangerous thrombophlebitis arising out of a cellulitis are infinitesimally small compared with columnar mucous membrane infections which have been traumatized by labour or operations. Witness the high incidence of thrombophlebitis following operations upon the stomach, bowels, appendix, nose, mastoid, and uterine cervix. It was demonstrated in a previous article[1] by me that thrombophlebitis is three times more common following subtotal hysterectomy than following total hysterectomy, because of the residual diseased mucous membrane of the cervix. It has been demonstrated[2] also that septic haemorrhages following cervical operations are due to unrecognized low-grade infections of the cervical mucosa, through which the repair sutures penetrate. In the same way tears and trauma of labour upon a diseased cervical mucous membrane are the predisposing immediate causes of thrombophlebitis in the majority of puerperal cases, though some cases arise out of the direct infection of the truncated thrombus-plugged vessels of the placental site.

Thrombophlebitis, from whatever cause, is an insidious disease, and, with the exception of cardiac and cerebral primary thrombophlebitis, it is recognized only by its complications. This is particularly true of pelvic thrombophlebitis. In an involvement of the pelvic vein, though one may suspect the presence of a thrombophlebitis by temperature and elevation of pulse-rate, yet it is singularly free from symptoms. And there will always remain a good percentage of cases without either symptoms or signs, in which the diagnosis can be made only by an embolic complication. And above all these, there will still remain a small percentage of cases of acute pyaemic infection with high fever and chills, and the still fewer cases of fulminating deadly anaerobic streptococcus putridus infections. These latter were common 25 years ago but fortunately are relatively rare with the advances in obstetrical technique. These cases were first demonstrated by Schottmüller[3] and later confirmed by Otto Schwartz.[4] So it is seen that the vast majority of cases of pelvic thrombophlebitis are symptom-free. The veins commonly involved are the uterine and the ovarian. So long as the disease remains local there is little to be feared. Complications of an embolic nature rarely occur in the more acute cases, but, on the contrary, are most common in the mild infections, or when the acute infections have reached a stage of

defervescence and recovery. These two factors make a fatal issue all the more tragic in that it is likely to occur when least suspected, or when hopes of recovery run high. The differences noted above between cases as regards the extension of the thrombophlebitis in insidious cases cannot be too forcefully emphasized. In the pathological museum at McGill are specimens of pelvic organs from patients in whom death occurred 2 or 3 months post-partum in which every vessel of the uterus and pelvis is filled with thrombus, and others from patients in whom death has occurred by pyaemia, in which the thrombus is minimal and the phlebitis maximal in quantity and extension. Of course the former is much the more dangerous. Few patients die nowadays owing to the primary infection in cases of thrombophlebitis; they nearly all die owing to the mechanical effects of embolic arterial block.

Embolism

Embolism from a primary pelvic thrombophlebitis always occurs in the lungs. The consequent infarct may be large or small, depending upon the size of the occluded blood-vessel, which, in turn, is determined by the size of the embolus. The base of the infarct is always towards the pleura and is always accompanied by a pleurisy. The site of the pulmonary infarct will determine the character of the symptoms. It will save many mistakes if one assumes that every acute pain in the chest during the puerperium, or after operation, is embolic in nature until it is proved not to be so. Involvement of the parietal pleura is usually indicated fairly accurately by the site of the pain. But this is not so when the diaphragmatic pleura is involved. In such patients the pain may be referred entirely to the abdomen, causing rigidity and splinting, or the pain may be referred entirely to the shoulder of the affected side, causing one to suspect biliary involvement or other subdiaphragmatic disease. Time generally clears up the diagnosis. Friction rub can usually be detected, and, in large infarcts, dullness and changed breath-sounds. In diaphragmatic pleural involvements these signs may not be detectable to confirm our suspicions. Small infarcts are much more common than any of us assume and are seldom detected, though often suspected by the wary clinician. The chest symptoms vary with the size of the infarct, from a slight stitch in the side to a seizure as if the chest were in a vice, or sudden death by occlusion of the pulmonary artery

at its bifurcation. Complications may arise as a result of the pulmonary infarct. A secondary thrombophlebitis may now begin to spread towards the heart, from the infarct along the pulmonary veins, and if, unfortunately, a small embolus should detach itself from this thrombus it will have ready access to the left auricle and ventricle, and will have gained the general circulation. When this occurs there is not an organ of the body that is not open to its reception. We have seen 3 cases of coronary embolism, 4 cerebral, 1 optic, 5 renal, 1 splenic, and 3 mesenteric. We must infer that many small emboli strike areas of less importance, such as muscle, for example, and are never properly diagnosed.

Much more interesting complications may arise other than embolic out of a primary gynaecological or puerperal pelvic thrombophlebitis. The most interesting is a remote metastatic thrombophlebitis. The common site of implantation of such a metastatic involvement is in the veins of the left leg. How does this occur, when the lungs are always interposing their fine filter of capillaries?

The method is simple. There are two processes.

1. There is a tendency in the majority of pelvic thromboses to liquefy. This liquefaction begins as a minute point and spreads. The contents of this vomica consist of micro-organisms and broken-down blood-cells and fibrin. When the vomica reaches the surface of the clot and bursts, a flood of this infected detritus is liberated into the venous circulation. The consequences will depend upon the nature of the organism in this flood, and the results may vary from a severe chill and pyaemia, in the very severe cases, to metastatic thrombophlebitis in the mild infections. Fortunately, the severe pyaemic cases are relatively rare as compared with former years of technical inadequacy. But the milder types are still all too common.

The contents of such a liquefied vomica are in such a fine state of division that the particles are smaller than a red blood-cell, and can pass through the pulmonary circulation without arrest, or, if arrest occurs, the involvement is so slight as to pass unnoticed. In the very severe infections septic pneumonia may follow, but in the vast majority of cases the infection passes through the lung without recognizable complications and reaches the general circulation. The result will be a metastatic thrombophlebitis.

2. The second method by which metastatic thrombophlebitis

can occur is due to a few organisms from the primary pelvic focus getting free into the general circulation. In a monograph on puerperal infections published in 1932,[5] it was pointed out that it is probable that in every case of local infection some few organisms gain access to the general circulation but, in most instances, they probably are soon disposed of. One cannot denote these sporadic systemic invasions as septicaemia. Septicaemia implies not only blood invasion but persistence and division and multiplication in the stream. The invasions under discussion are sporadic and probably short-lived. The fate of these organisms will depend upon many factors: their virulence, their diffusibility, their relative innocuousness, their preparation of the body in antibodies. We do recognize clinically, however, that when a certain degree of tolerance is established—call it symbiosis—organisms may live in the circulation for very long periods, even years, and, in favourable circumstances, may localize. In thrombophlebitis cases the localization will occur in sites presenting conditions similar to those of the primary focus of infection in the pelvis, and those sites of localization for metastatic thrombophlebitis are usually in the veins of the left leg. At once we ask the questions: (i) Why are the metastases of a thrombophlebitis thrombophlebitic in character? and (ii) Why are the veins of the left leg so commonly involved as compared with those of the right?

I think the popular belief concerning metastatic involvement is that of a microbe which, dislodged from its primary site into the circulation, seizes upon the first tissue contacts to rehabilitate itself. This, of course, is not true. Microbes have a predilection for certain tissues, and those tissues are those which most closely reproduce the condition where it found its foothold in the body of its host. This predilection is a very powerful factor in determining the course and complications of any disease, and it distinguishes one microbe from another in the selection of a tissue. This power of selectivity of microbes is the very essence of specificity of disease. Why does the organism of anterior poliomyelitis always choose the anterior horn of the spinal cord? It must gain access to the cord through the circulation, and, therefore, has a wide choice, but predilection for a certain tissue, owing to a dietetic biochemical change, determines the choice. So it is in thrombophlebitis. The organism of the disease, inured to an intravenous environment, selects a site of similar character. Varicosities are most common in the lower extremities owing to gravity, and are more

common in the left leg than in the right owing to the left iliac vein passing under the iliac artery to reach the vena cava. This factor, aided by an inherited venous weakness, predisposes to varicosities, and where varicosities occur there is a slowing down of the flow owing to the broadening of the channel and a consequent proportionate poor nutrition and deposition of fibrin to restore the lumen. Such varicosities offer a nidus of attraction that the vagrant microbe is quick to seize.

Not all cases of saphenous and femoral thrombophlebitis, however, are of a metastatic nature from a primary focus elsewhere. Some are primary in the leg, due to trauma or many other causes, but appearance of a thrombophlebitis of the left leg after operation, or in the puerperium, should make one suspicious of the development as an indication of an unrecognized primary focus in the pelvis. Direct extension from the uterine veins into the common iliacs, and thence against the stream down the leg, is a rare, very rare occurrence, and is accompanied by such widespread circulatory disturbance in the abdomen and lower limb that one could not miss its grave significance. In the vast majority of instances merely the unsupported saphenous is involved, and the end-result is not greatly incapacitating. Of course, it need hardly be noted that each such secondary metastatic focus becomes an additional menace from which a small or large embolus may take its departure on its way to the lungs.

Phlegmasia Alba Dolens

This disease has taken on a new significance now that its pathology is properly understood. With the proper knowledge of its *modus operandi* its distribution has been appreciated, and a new chapter in pelvic pathology has been written. We will endeavour to convey in as short a space as possible the extension, clinical importance, and pathology of the disease. Among the early obstetricians the term ' phlegmasia alba dolens ' had a relatively narrow application, merely to those cases of permanently large white leg arising out of labour. We now know that the pathological process at the bottom of that disease is an infection and blocking of the minute lymph channels of the affected parts. It is now recognized that the pathological process, like other less specific infections, may remain confined to the organ primarily infected or may extend in many directions other than into the legs, from the primary focus in the pelvis. This is the new broad concept which has arisen out of the new pathology.

The primary site of infection is generally the uterus or cervix, or both. Whether the cervix is the more common primary site, the uterus being secondarily involved, or whether the reverse is the truth, has little clinical importance, and is impossible, in our present state of knowledge, to determine. One clinical fact is certain, however, and that is that both cervix and uterus are usually simultaneously affected, though there are some exceptions, and in those exceptions the uterine and the cervical would seem to be about equal numerically.

Pathology.

The cause of phlegmasia alba dolens is an infection. We are of the opinion that the organism is a specific one, or at least one which, though having a common parenthood with other organisms, has acquired a specific individuality. This opinion is held because the disease has specific characters wherever found, and any differences are attributable to the terrain and not to microbic versatility. Just as a thrombophlebitis finds its specific tissue of predilection in the vein and thrombus, so the organisms of phlegmasia alba dolens find their normal habitat in lymph and lymphatics. The two diseases, when this distinction is recognized, run almost parallel courses, and their complications are equally interesting.

The pathological entity is a blockage to the normal flow of lymph by occlusion of the lymph capillaries by lymph coagulation and reactionary multiplication of the lining cells of the lymph capillaries. In the first stages there is the fluidity of cell division, which, after prolonged duration, gives place to the fixity of connective tissue. The end-result is a degree of permanent lymph block, the extent and degree of which will depend upon the extension and duration of the disease. Also, the degree of resolution will depend upon the same circumstances of extension and duration. It would be easy to present beautiful photomicrographs of the lymph status in the myometrium, but in these times of financial stress this becomes an impossibility and will be reserved for a future occasion. The disease is commonly confined to the uterus and the cervix, but it may extend thence along any of the usual lymph channels from this common primary focus of infection. These extensions may be into the broad ligaments and parametrial tissues generally. Thence, by continuity, into the lumbar region, legs, anterior abdominal wall and remote metastatic patches anywhere in the body. It is thought that these metastases are always found in lymphatics,

but of course this is difficult to prove, though in confirmation of this opinion the metastases of observed cases have always been in the dermal and subdermal tissues.

Common Clinical Manifestations.

The commonest pelvic manifestations of this disease are found in the so-called chronic metritis and chronic cervicitis. There is a paper on chronic cervicitis in the February issue of this journal in which the pathological process is defined.[6] It may be well to repeat some of the details to maintain continuity of this subject. It is now known that chronic cervicitis, as distinguished from chronic endocervicitis, is a disease of the fibro-muscular tissues of the cervix, complicated by numerous Nabothian cysts. The dimensions of the cervix may reach such proportions as to fill the vault completely. The cervix is hard, nodular, pearly white, and cyanotic. This disease is usually a complication of labour or abortion, and in the early state of the infection the uterus is soft, has a retarded involution, is frequently tender, and the cervix is similarly involved. As time goes on this softness of subinvolution gradually passes into the fixity of adult tissue, and we have then the commonest of all uterine diseases, the so-called chronic metritis, a large, symmetrical, hard uterus, with thick walls and tender to the touch on bimanual examination. There may be a slight or marked degree of fixation, depending upon the degree of extra-uterine extension and its duration. The cervix is usually similarly involved, and so frequent is this association in a common involvement that a chronic cervicitis is a fairly constant index of a similar involvement of the corpus. Such is the pathology of chronic metritis and chronic cervicitis. Sections of the uterine wall and cervix, at this stage of induration and enlargement, show a preponderance of fibrous tissue, a lack of destruction of the redundant elastic tissue of pregnancy (as outlined in my monograph upon vitreous degeneration of uterine elastic tissue: "Royal Victoria Hospital Studies, 1913"),[7] and a great deposit of solid lymph in a state of stasis about the blood-vessels and between the muscle bundles. Is there an accompanying venous stasis? It would seem logical that such would be the case, but this is a difficult matter to determine. One would naturally assume that the thin walls of the veins and the low venous blood-pressure would be influenced by this extra-vascular tension to a greater degree than would the arterial system. If one may judge from the frequent cyanosis of the

cervix in chronic cervicitis, then venous stasis becomes an added factor. It seems certain that the disease, once established, is tenacious and long-lived in its activity to produce progressive changes. Chronic metritis and chronic cervicitis have no specific symptoms because these organs are almost devoid of sensory nerves. In this initial stage the infections which eventuate in chronic metritis and chronic cervicitis are of low-grade character. They are seldom diagnosed and, at most, present a mild, short-lived systemic reaction, of which, owing to lack of localizing symptoms to direct attention to the area affected, the true nature of the disease may escape the most expert clinician. Consequently the disease is usually diagnosed only years after its inception. But that the disease remains active locally over a very long period after all systemic reaction has disappeared is shown by the permanent enlargement of the body of the uterus and cervix. This enlargement permits of two possible explanations. One, that it is a permanent subinvolution with fixation of the uterine tissues in a post-partum permanent state of imperfect destruction and absorption of the tougher elastic and fibrous tissues at the expense of the more specialized and consequently more delicate muscle fibres, as described in my monograph; or, secondly, that the disease is a very tenacious one, exercising a slow local stasis and fibrosis in the affected organs, owing both to microbic toxins and progressive lymph block, due to fibrotic changes. Hence these diseases are insidious, and seldom recognized until some intercurrent condition directs attention to their abnormal state. A feeling of weight in the pelvis, leucorrhoea, and abdominal pain after intercourse are some of the infrequent symptoms. Haemorrhages, if they occur, are purely incidental and have no relation to the disease. It has been an error to attribute haemorrhages to this condition. Usually the disease has been in existence unrecognized until the uterine haemorrhages drew attention to the metritis, and what more natural than to attribute the haemorrhage to the local disease? Really the haemorrhage in the vast majority of cases is of extra-uterine origin.

If the disease, when confined to the body of the uterus and cervix, is relatively symptom-free in the vast majority of cases, it is quite otherwise when extension has spread beyond the uterine confines. In the early phases of this stage of the disease the parametrium may be slightly and locally affected, or markedly and diffusely. The course of the disease, as frequently observed in its parametrial extension, is very interesting. The

complaint of pain attracts one's attention to the pelvis, and, more particularly, to the affected side. On palpation one finds the well-recognized bimanual signs of a one-sided pelvic cellulitis. Repeated examinations at intervals of two or three days show that the process is slowly extending in all directions, out to the pelvic wall and laterally as well, and this process of extension goes on until the whole pelvic cellular tissue becomes involved. One interesting fact is disclosed by this observation, and that is that the disease progresses in the pelvis, as one can observe more readily in the phlegmasia of the leg, both in the direction of and against the lymph stream. The end-result is a more or less complete block of lymph flow and a consequent tremendous increase of intercellular and intracellular plasma; in other words, a lymph stasis, with a slow escape of the inorganic elements of the lymph and a residue of the cellular elements. The vaginal vaults become of cartilaginous hardness and the organs become decidedly fixed. The condition corresponds to any other parametritis in the early stages of the disease but later it is marked by its persistence, hardness, pain, tenderness, and more or less permanent fixation. The true nature of the disease may remain in doubt but should be suspected. Extension may now be in one or all of the following directions: into the leg by the inguinal region, into the buttock by the sciatic notch, up the posterior pelvic wall into the loin, or into the anterior abdominal wall by the anterior layer of the broad ligament.

Involvement of the leg is probably the commonest extension, perhaps because it is the most easily recognizable. Pain is frequently felt for days in the region of Poupart's ligament, then swelling of the leg begins, and the disease is now most frequently diagnosed as a thrombophlebitis, and this mistake may persist if only the deep lymphatics are involved. If the disease appears on the skin surface, as it not infrequently does, the skin about Poupart's ligament appears white, with discrete sweat glands, and the margin of the diseased skin is elevated about a quarter of an inch above the normal. To the touch the affected skin feels hard and pits only on prolonged pressure, and the impression thus made lasts for a very long period. The margin of skin involvement may advance down the leg or may spread up the abdomen, or in both directions simultaneously. In one such case the advancing margin of lymphatic block had a pale pink colour, and each day one could measure the spread. The degree of involvement of the lymphatics of the leg as the

disease spreads from the pelvis will determine the amount of back pressure and consequent swelling of the leg. Sometimes only the deep lymphatics are involved; in others, only a segment of the whole thickness of the leg may be involved. The disease may not come at all to the skin surface. There are vagaries of any disease. Contrasted with thrombophlebitis, the pain is out of all proportion to any thrombophlebitic case. It is of a dull boring character, due, we think, to involvement of the nerve trunks. The pain is often referred to the trunk endings. When the disease extends up the posterior pelvic wall, pain in the loin becomes a most distressing and persistent symptom.

In one case, in which it was possible to watch all its slow development, after involvement of the leg the disease spread slowly up the posterior wall, and one could watch its progress by the advance of the pain. Another case, which had had both legs involved, causing the patient to be in hospital for 4 months, now, 12 years after that complicated puerperium, suffers pain so severe in both legs as to make her a veritable permanent martyr. The tragedy of these cases lies in their persistence of the symptoms and swelling, and the longer the activity of the disease lasts the more permanent and widespread will be the block, and the more persistent will be the pain.

Metastatic phlegmasia is a rather rare complication. It occurred in two cases. The metastases were all in the cutaneous and subcutaneous tissues. They developed patches—white, elevated, indurated skin, similar to the involvement of the thigh described above. One patient had a patch on each upper arm, and one on the chest near the axilla. The other had involvement of the skin on one breast and of the base of the neck. These patches cleared up when the primary disease became quiescent. They were circumscribed in size, and were not particularly painful. Doubtless a few organisms got free into the circulation and set up these metastases in sites of predilection. Doubtless, also, many such metastases could occur in the deeper tissues, remote from the primary site, causing deep-seated pain, but we doubt whether this could ever be diagnosed, though they might be suspected.

Treatment.

It would be superfluous to enter into the treatment of thrombophlebitis. But a word about the treatment of phlegmasia is necessary. It is important that the diagnosis should

be made as early as possible. When the disease is acute and limited to the uterus and cervix, it is so insidious that it would probably escape attention in its incipient stages. The only sign would be uterine subinvolution and a degree of tenderness and a remarkable paucity of symptoms. But these alone would be insufficient to warrant anything but a suspicion of the nature of the disease. When the condition has passed into the chronic state, topical treatment is absolutely futile, and as the disease is usually symptom-free, one need not introduce any active therapy. We believe that any unnatural bleeding is purely incidental. Operations upon the cervix are futile also, and are strongly contra-indicated. The limited application of cervical surgical procedures in these conditions were definitely outlined by Dr. Anderson and myself in a paper which appeared in the February issue of this journal.

Sterility is the rule, but should a pregnancy supervene and one is careful in one's technique at delivery, and every effort is made to hasten the involution of the uterus by uterine stimulants, the diseased uterine walls may return to their normal size and state. I have had several such cases, one of the patients by mistake being kept on ergot for a dangerously long time, and when examined the uterus had reached a high degree of superinvolution. But then, she had been on ergot for over 3 months—by mistake, I hasten again to add. One cannot advocate such a vigorous treatment in spite of the good result. And yet, prior to conception, her uterus and cervix presented a most marked case of chronic metritis and cervicitis.

When the extra-uterine extension has developed, the severity of the pain soon draws one's attention to the disease and causes one to suspect its character. But it may be only when the disease becomes superficial that a positive diagnosis may become possible. However, as in any other diseased condition, every means of heightening the patient's resistance should be used, chief among which are the reticulo-cellular activators, repeated blood transfusions, or small doses of insulin, or small doses of thyroid, or all three, under careful supervision; and a well-regulated diet, sunshine, natural or artificial, and heat. Local heat should be used, but high frequency is contra-indicated except when the disease has become definitely quiescent. Pain, which is such a distressing symptom of the boring character, should be assuaged by suitable therapy, and by a frequent change of the drug employed.

Prognosis.

The prognosis is good as regards life. I have seen but one case of phlegmasia in which the patient died of the disease. That was the case noted above with the pink advancing margin both up the trunk and down the legs. This case had some of the characters of a subacute erysipelas, and decidedly those of phlegmasia, but it was by far the most acute case that had ever come under my observation. When we come to the question of prognosis as regards complete restoration of function, it behoves one to be guarded. Sterility is the rule in severe cases of uterine involvement, but just as there are all degrees of involvement, so there will be all degrees of hindrance to conception, and effective implantation may also be proportionately changed where conception has taken place. Permanent fixation, or a degree of loss of mobility, is a not infrequent consequence of a major or minor extension beyond the uterus. There are all degrees of permanent pain in the loin and legs. Patients describe this as boring in character, and interference with rest and sleep is the common consequence.

The degree of permanent swelling of the leg will depend upon the completeness or incompleteness of the lymph block in the hip and thigh region and the duration of the disease. These two factors need some elucidation. First, many of the leg involvements affect only a segment of the leg's circle; others affect only the deep lymphatics; others, only the superficial; and in still others, the disease affects all of the leg tissues for a distance about the thigh. The oedema will depend upon these factors. Secondly, by analogy with veins it is thought, though it cannot be confirmed, that lymphatics involved mildly for a short period may be restored to full or partial function. The evidence in support of this is so far meagre but fairly convincing. One of my patients, of fairly recent date, developed what was thought to be a thrombophlebitis of the left leg, following a low Caesarean section. She ran a mild temperature and elevation of the pulse-rate, which gradually disappeared. The leg became markedly swollen, and the pain was severe in the calf and down the region of the sciatic nerve. Later the diagnosis of acute phlegmasia was confirmed. To-day, 6 months later, the oedema of her lower leg has completely disappeared, though her hip and buttock on that side have remained considerably larger than the unaffected side. My attention was drawn to this asymmetry by the patient herself. This will now probably be a permanent state. By the location of this swelling it is prob-

able that the disease reached the buttock through the sciatic notch. From this case, I think, we can be convinced that, by the disappearance of the oedema in the affected limb, a great many of the lymphatics previously blocked were restored to full or partial function, either by absorption or canalization of the block, or by compensatory dilatation of parallel channels in unaffected areas.

Per contra, when by prolonged duration of the disease the fluid cellular and lymph contents become converted into the fixity of connective tissue, any hope in remedial relief is doomed to ultimate disappointment. As a last and pregnant thought, let us bear in mind that all the clinical evidence points to an activity of the disease long after we are likely to assume that a cure has been effected. In this respect the specific organism of phlegmasia is such by attenuation of one of a common family, or a degree of incomplete corporeal symbiosis is maintained for a long time until the symbiosis process has been made complete, and the organism's activity, from that moment on, becomes neutralized and innocuous.

To sum up, both pelvic thrombophlebitis and phlegmasia alba dolens are indistinguishable clinically in their incipient stage, rarely diagnosed, though often suspected when temperature and pulse-rate show indications of a symptom-free infection following operation or labour. Thrombophlebitis, in the vast majority of cases, is diagnosable only through its complications of embolism or metastases; phlegmasia is recognized only when extensive involvement of the pelvic cellular tissues, or those of the leg, has taken place. Thrombophlebitis is fatal in a goodly percentage of cases, by virtue of its embolic mechanical accidents; phlegmasia is rarely fatal. Thrombophlebitis has few chronic sequelae except swelling of a limb or serious damage to lung tissue; phlegmasia has frequent, distressing sequelae of constant pain in the affected part, and permanent lymphatic block, causing plasma oedema of the tissues below the block. The permanent incapacity of thrombophlebitis is slight; that of phlegmasia may amount to almost total permanent incapacity in the extensive and prolonged cases of infection.

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A Case of Puerperal Retention of Urine causing Traumatic Rupture of the Bladder and Death

BY

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WITH PATHOLOGICAL NOTES BY

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ON July 7th, 1939, I was called up shortly after midnight by Dr. B. who said the patient he wished me to see was Mrs. E. S., wife of one of his panel patients. She had been referred to him by a municipal clinic on account of albuminuria. He did not find any albumin in the urine, and sent her to the municipal maternity home for antenatal supervision and confinement, asking them to call him in at once if albuminuria or any other abnormality developed. She was, when sent to him on June 6th, aged 34, pregnant for the fourth time, about 37 weeks, and had a history of three previous normal full-time labours. She was very obese.

He heard nothing more of his patient until 10 p.m. on July 6th, when he was asked to see her in the municipal maternity home, because she was ill. He found her very ill, with a pulse-rate of over 120, anaemic and dyspnoeic. The history was that she had been delivered normally 10 days before; for the first few days of the puerperium there was considerable lower abdominal pain, but not any since. The temperature chart had not been above 99°F. except once on July 4th, when it was about 100°F. Dr. B. asked for the ward report book, and found that the temperature had exceeded 100°F. more than once, though this did not agree with the chart; he also found that a doctor in the public health service had seen the patient 2 days before without referring to him. The chart of involution showed a descent of the fundus from 6 inches to 2 inches above the pubes. On examining the abdomen, he found a firm abdominal swelling arising from the pelvis to a point 2 inches above the umbilicus, broad and symmetrical. There was, therefore, a gross discrep-

ancy between his findings and the involution chart. The swelling was not tender. On vaginal examination there was considerable bulging of the anterior vaginal wall, and a smaller bulging of the posterior wall. The examining finger could not reach the cervix. A consultant was called in, but he was no longer in charge of hospital obstetric beds, and since the patient was considered to require hospital and possibly operative treatment, Dr. B. called me in, the other consultant agreeing to this. All this history was given to me over the telephone by Dr. B., and I then asked him if there was any question of the bladder being distended. He said that he had asked about bladder action as soon as he saw the abdomen, and was assured it was normal. A sister in the home had then passed a catheter on his instructions and obtained nothing but a little blood-stained fluid.

I went out and saw the patient, confirming the physical signs given by Dr. B. The tumour seemed firmer than a distended bladder, but I was not satisfied about this, and, having arranged for the patient's transfer to Leeds Maternity Hospital, I went in and awaited her arrival there. She was admitted at 1.45 a.m. on July 7th, and then, with the aid of my house surgeon, who held the labia apart, as she was extremely obese, I passed a catheter and obtained 37½ ounces of urine deeply stained with blood. I then changed the catheter for a self-retaining instrument with a clip, and, before her death at 5 p.m., release of the clip at intervals had obtained altogether 143½ ounces of urine.

On admission to hospital her temperature was 97.4°F., the pulse-rate 136, and the respirations 28. She answered questions with an effort, slurring her words. By 8.30 a.m. she was drowsy, but the general condition appeared better. At 11.30 a.m. the tongue was brown and coated and she was vomiting acid brownish fluid. At 1 p.m. she was in coma. By 2 p.m. the pulse-rate had risen to 160, and it was 176 before death at 5 p.m.

Investigations. Specimens taken on admission.—Blood: Haemoglobin 55 per cent, red cells 4,000,000, colour index 0.7, white cells 12,100, red cell size 7.3, polymorphonuclear leucocytes 86 per cent, lymphocytes 12 per cent, L. hyalines 2 per cent. Blood-urea, 268 mgm. per 100 c.c. Blood-sugar, 0.133 per cent. Cerebro-spinal fluid, Wassermann reaction negative. Blood-pressure at 3.45 a.m., 150/80; at 8.30 a.m., 195/100; 12.30 noon, 210/125; 1.50 p.m., 170/95.

Fluids taken after admission.—By the mouth, exactly 50 ounces of water and lemonade; 1 litre intravenous dextrose 20 per cent and some dextrose 5 per cent.

CONDENSED POST-MORTEM REPORT.

External appearances: An obese woman with oedema of extremities and face. Abdomen: On section the abdominal cavity contains a small amount of free fluid, turbid, and reddish in colour. The bladder is full and extends to the level of the umbilicus; its peritoneal reflexion is about 4 inches above the pubic symphysis. The peritoneal surface of the organ shows numerous large ecchymotic areas. The cavity contains about 100 ounces of bloody urine; the blood is mostly haemolysed. The mucosal surface does not show any evident inflammatory change, but there are numerous tears due to tension, involving both the mucosa and musculature and extending almost to the outer coat. These tears correspond to the bruising, noted above, of the outer surface. The uterus is lifted to the same level as the bladder. The cervix admits a finger. On section in the posterior mid-line, the cervix is found to be almost fully dilated, blackish in colour but without foul smell. The uterine cavity contains some blood and a very few placental relics. There is not any odour of gangrene and the musculature is normal in appearance and texture. The Fallopian tubes and ovaries are normal. Kidneys: The organs are about $6 \times 4 \times 3$ inches. On section there is much medullary and cortical congestion, but the parenchyma is soft and pale. The capsules strip readily, but leave numerous pin-point haemorrhages. A slide was made of the kidney and the histology is that of an acute toxic nephritis. The glomerular tufts and the interstitial vessels show gross engorgement; the tubular epithelium shows gross cloudy swelling; the tubules contain a few hyaline casts. The suprarenals are normal. The stomach is filled with muddy fluid with little or no smell. The pyloric mucosa is much engorged. The intestines, large and small, are filled with gas apparently the result of obstruction by the bladder and uterus at the pelvic brim, otherwise the organs are normal. The liver is normal in size, pallid, and a few punctiform subcapsular haemorrhages are present. The spleen is enlarged, $8 \times 5 \times 4$ inches, and pale. The pancreas is normal. Thorax: There are no adhesions, but there is a little free fluid on both sides. Right and left lungs show gross basal congestion and oedema, mild apical oedema. Areas of consolidation are absent. Heart: The organ is pale, flabby, and almost exsanguinated. The cranium: the cerebro-spinal fluid shows no evidence of tabes dorsalis.

Anatomical diagnosis: Gross retention of urine with tension trauma of the bladder. Toxaemic changes in the abdominal viscera.

There are various points of interest which arise from this case.

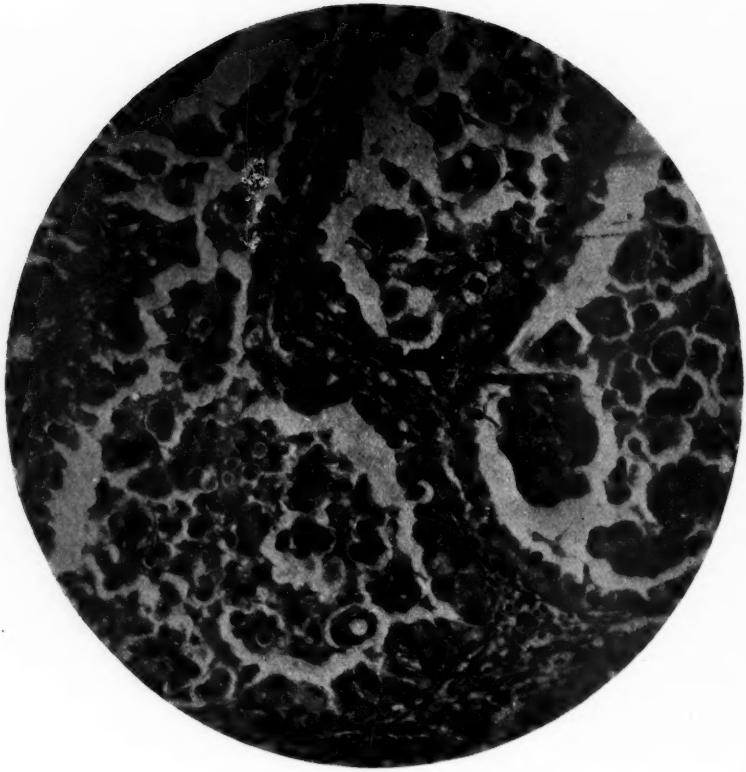
1. Maternity homes where there is not daily medical supervision are undesirable. The private midwife is hedged about so that she cannot move a step without notifying a doctor or the local supervising authorities or both, while she is at any time liable to inspection by the superintendent of midwives. This home, with a certified midwife in charge, was apparently so little supervised that it was possible for a patient to be in and ill for ten days after her confinement without her own doctor being informed, in spite of his specific request to be told of anything abnormal in the case.

2. The retention of urine, which no doubt dated from her confinement, was not detected in spite of the suggestive lower abdominal pain. This was probably due to the fact that she had overflow. I believe that nurses almost never diagnose retention if there is overflow.

3. The involution chart was a product of either a very imaginative or a very ignorant nurse.

4. The conduct of the matron in asking a Public Health doctor to see the patient in the circumstances was remarkable; as was the doctor's, especially as he apparently did not achieve a diagnosis or advise treatment.

5. Undiagnosed retention of urine is probably not a great rarity, which usually cures itself. Death from multiple tears of the enormously distended and paralysed bladder with accompanying toxaemia, however, must be rare. It appears very likely that had the retention of urine been discovered in reasonable time, say within the first 24 hours, the patient would have survived.



SECTION OF CERVIX

F.S.]

Carcinoma of the Cervix in a Girl Fifteen Years of Age

BY

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CARCINOMA of the cervix before the age of 20 is so rare that it seems advisable to report this case which came under my care at 15 years of age. The registrars of St. Mary's Hospital, Manchester—now Surgeon-Lieut. Rickards, R.N.V.R., and Capt. Racker, R.A.M.C.—kindly searched through the literature for me. They have been able to find reports of 17 cases of patients at, or before, 20 years of age, but of these several do not seem to be substantiated.

Kohlaas[1] published a case in a patient at 16 months of age and the histological findings suggest that it commenced as a carcinoma of the cervix. Another at 16 months of age was reported by Kehrer and Neumann[2] as a case of carcinoma of the genital tract, but from the pathological report it seems unlikely that the growth originated in the cervix. Englehorn[3] reported a case of carcino-sarcoma at 2 years of age. The diagnosis was not confirmed as the preparation was poor, but even if the diagnosis is correct it is not claimed as a case of pure carcinoma of the cervix. Another case was reported at $2\frac{1}{2}$ years of age by Adams,[4] but the committee of the Royal Society of Medicine thought it to be a teratoma rather than a carcinoma.

Glockner[5] reported a case at 7 years of age, and the diagnosis was confirmed by Robert Meyer. Ganghofer[6] reported one at 8 years of age. The histological type is not given, but this is 1 of the 3 cases under 20 years of age accepted by Gayraud[7] when reporting on the literature in 1911. Macdonald[8] reported a case in a girl of 10 years of age. Morse[9] also reported a case at 10 years of age as carcinoma of the genital tract, but from the pathological reports the growth does not seem to have originated in the cervix.

Bonner[10] had a case of papillary adeno-carcinoma in a girl

13 years of age. Two cases at 16 years of age are reported by Ludwig[11] and Glass[12] respectively. Schauta[13] is reported by Englehorn as having found this condition in a girl of 17 years of age, and Frankel[14] in a girl of 19 years of age. Tschop[15] and Eckhardt[16] found it in girls under 20 years of age, and these, with the case of Ganghofer, are the only ones accepted by Gayraud in 1911. Finally, Darnall[17] reports one in a coloured girl 20 years of age.

So far, then, as the cases can be judged from the written description, we can find in the literature only 12 cases of carcinoma commencing in the cervix at, or before, the age of 20 years, and not one of these was in the British Isles. Taking these in chronological order they are: Kohlaas at 16 months; Glockner at 7 years; Ganghofer at 8 years; Macdonald at 10 years; Bonner at 13 years; Glass at 16 years; Ludwig at 16 years; Schauta at 17 years; Frankel at 19 years; Darnall at 20 years; Tschop under 20 years; Eckhardt under 20 years.

It seems, therefore, to be a duty to report the following case which occurred in a girl only 15 years of age, and which, so far as I can tell from the literature, makes it the 6th youngest on record.

Notes on the Patient

J. H., 15 years of age, was admitted under my care at St. Mary's Hospital, Manchester, on October 19th, 1937, suffering from epimenorrhagia. Menstruation had commenced when she was 13 years of age and had been frequent and excessive from the commencement, generally occurring at fortnightly intervals and lasting for 6 days. For 7 weeks prior to admission to hospital there had been continuous bleeding.

Before admission she had been sent to the Hormone Clinic at St. Mary's Hospital by her own doctor on account of this epimenorrhagia, and, as it is against our custom to examine *per vaginam* very young girls in this department, she was treated with bi-weekly injections of progestin for 3 months. As there was no improvement, she was admitted to one of my beds so that she could be examined under anaesthesia, and this was carried out on October 25th, 1937.

There was a well-marked hymen, and I had difficulty in inserting one finger into the vagina, but when the hymen was dilated I was surprised to find on the anterior lip of the cervix a large irregular friable growth. This overhung the posterior lip,

and I had some difficulty in fixing this lip with a vulsellum forceps, but eventually found it to be quite free from growth. The growth on the anterior lip was circular and about 1½ inches in diameter, while the external os was linear in appearance, more like that of a parous woman. Pieces of tissue were removed from this growth and were subsequently reported upon by the pathologist as being an adeno-carcinoma.

On November 4th, 1937, 40 mgm. of radium, screened with 1 mm. of platinum, were inserted into the uterus, and 2 plaques each of 35 mgm. of radium, screened with 0.5 mm. platinum and 1 mm. silver, into the fornices. This was retained for 22 hours and the same dose repeated a week later and again 3 weeks later, making altogether a treatment of 7,260 milligram-hours.

The growth responded very quickly to the radium treatment, and in February, 1938, the cervix was quite healed and smooth and the patient felt very well. At that time a course of deep X-ray therapy was commenced and continued for 20 sittings.

In April, 1938, I readmitted this patient to the Royal Infirmary with rectal symptoms, and an examination revealed an anular growth of the rectum at the level of the cervix. The cervix itself was still quite small, and looked healthy. Professor Morley kindly transferred her to his surgical ward, and on May 3rd, 1938, an exploratory laparotomy revealed an anular growth of the sigmoid with involvement of the iliac glands on both sides. Extirpation was impossible, and only a colostomy could be performed. The patient's condition progressively deteriorated, and she died on June 7th, 1938.

Comment

The obvious criticism of this case is that 3 months were wasted while the patient had treatment in the Hormone Clinic, and I have to acknowledge the truth of this. On the other hand it must be remembered that we treat a large number of young girls for menorrhagia of puberty, and that to examine all of these in an out-patient department may do much psychological harm. The alternative is to examine them under anaesthesia, but to do this in every case presenting itself with this common complaint seems hardly to be justified even by this case of carcinoma when we remember its extreme rarity and the fact that treatment at this early age is not likely to effect a cure even at a very early stage of the growth.

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An Unusual Case of Carcinoma of the Body of the Uterus

BY

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MISS G. J., aged 47, a schoolmistress, was referred to me on December 30th, 1939, for uterine haemorrhage. The menarche was at the age of 11½ years; she was unable to remember being free of loss since then for more than a day or two, except for several intermissions after X-ray therapy, which will be specified. She had what the radiologist described as a full sterilization dose for this bleeding in 1929, when she was 36, but without effect. Exploration of the uterus was not undertaken at this or at any other time. Further X-ray treatment was given in another town in 1930, once a month for 12 months. After this there was amenorrhoea for about 3 years. In 1933 haemorrhage started again, and she had 6 further doses of X-rays; amenorrhoea ensued for 3 years again. In each of the years 1936, 1937, and in 1938 she had further X-ray treatment, and after each course there was amenorrhoea for about 12 months. In spite of considerable effort to discover what dosage was given details could only be obtained of the 1938 treatment, which was as follows: a total dose of 700 R. was given to each of 4 fields, size 15 × 15 cm. Voltage, 200 K.V. F.S.D., 50. Filter, 1 copper and 1 aluminium. This was completed in July, 1938, and there was no further bleeding till May, 1939, since when it had been continuous; she was finding this tiresome.

Miss G. J. was very fat, possibly weighing about 16 stone. The obesity was most marked in the abdominal wall: over the right lower quadrant of the abdomen were several telangiectases. Anaemia was not obvious. On vaginal examination a mobile mass could be felt about the size of a normal uterus; owing to the obesity it was not accurately definable, and was thought to be the retroverted uterus.

In view of the long history I did not seriously consider the possibility of malignant disease, but I thought a curettage was

desirable, especially as it had never been done. The patient was anxious not to have operative treatment at the time, and so I suggested to her doctor that she should be treated with testoviron (8 doses of 10 milligrams at intervals of 3 days), advising him that if this did not give relief she should come in to hospital for curettage. In considering more radical treatment, I was loath to undertake hysterectomy by the abdominal route owing to the extreme fatness, and by the vaginal route because of the poor access. On the other hand, it appeared undesirable to give further X-ray treatment in view of the previous repeated doses, largely unknown, and the telangiectases. There remained the possibility of giving radium. A radiologist expressed the opinion that it would be safe to do this.

I heard nothing more of the patient until June, 1940, when her doctor rang up and said she had had no relief from the testoviron, and was now willing to be curetted. She was admitted to hospital and I curetted her on June 18th. A blood-count showed 5,600,000 red cells per c.mm. and 110 per cent haemoglobin. Examination under anaesthesia confirmed the findings on the previous examination. The sound passed $2\frac{3}{4}$ inches, and the curettings were scanty and did not suggest malignancy. The pathologist reported a few days later that the curettings were carcinomatous. By this time the patient had returned home, and I had to send for her again. On July 2nd I inserted 40 milligrams of radium into the uterine body and 80 milligrams against the cervix for 40 hours. Being still somewhat sceptical about the diagnosis, I curetted her again, but obtained only material described by Dr. Lissimore, the pathologist, as "fibroblastic granulation tissue." Endometrium was not obtained. On July 19th I inserted 40 milligrams of radium into the uterine body for 47 hours. On August 15th I heard from the patient's doctor that she had developed pain in the right iliac fossa, radiating to the thigh and through to the back. On October 2nd she died.

There were many remarkable features in this case: the prolonged haemorrhage without appreciable interval from the menarche until X-ray treatment was started; the administration of this treatment in ignorance of the state of the endometrium over a period of 9 years; the obesity and the telangiectases making satisfactory treatment difficult when ultimately undertaken. The following questions may be asked: When did the carcinomatous process start? May it have been associated with

excess of oestrin? (Oestrin estimations were not undertaken.) This appears unlikely as the curettings were scanty. May the repeated X-ray doses have had something to do with the development of the growth; or, on the other hand, may they have kept it in check over a period of years?

Finally, was it carcinoma of the body of the uterus which killed her so quickly, less than 3 months after treatment, although at the time of operation the growth seemed early? Evidence of infection or other pelvic disease which might have accelerated the issue was not present.

A Case of Ectopic Liver Tissue in the Newly Born

BY

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LESS than a dozen cases of solid tumour of the umbilical cord are recorded. Although this case is not strictly an example of neoplasm of the cord, the diagnosis from new growth could not easily be made clinically. Theories of aetiology can be measured against the detailed findings and are of more general interest. For these reasons a detailed report is given.

The maternal history was abnormal but probably unrelated to the foetal condition. The mother had had toxaemia in a previous pregnancy, and had also suffered from asthma since adolescence. Continuous asthma of a severe degree had been experienced for 2 days before admission and continued, despite the usual remedies, during the one day in hospital before delivery. Birth was assisted by the forceps when the head reached the perineum. The infant was cyanosed to about the same degree as the mother, but recovered rapidly after a few respirations.

A pyriform tumour, $2\frac{1}{2}$ inches in diameter, was found at the foetal end of the umbilical cord. The cord itself was oedematous, and the veins were dilated for 6 inches distal to the tumour. The surface of the mass was smooth and the contour regular. The consistence was firm, and fluctuation could not be elicited; on the other hand, the volume decreased slightly during steady pressure and increased after release of control. The mass was opaque. The narrow end passed into the umbilical opening so that the upper limit could not be defined, but impulse was absent when the infant strained. The tumour did not pulsate. Abnormalities other than the above were not found in the infant.

As the tumour breached the abdominal wall and was covered only by Wharton's jelly and the amnion, early operation was necessary to prevent the development of peritonitis. One day was allotted to permit the child to recover from the stresses of parturition.

At the operation, the matrix of the cord was desiccated and could be readily shelled off the tumour. While dissecting between the tumour and the caudally placed umbilical vessels a peritoneal sac was discovered. This sac was 1 inch long with a neck which would not admit the little finger, and was empty. On further examination of the tumour a second covering continuous with the muscular part of the abdominal wall was demonstrated. Finally a true capsule was encountered. At the apex of the mass a pedicle was formed which passed deep to the abdominal musculature but remained extra-peritoneal. This pedicle turned cranially, probably into the ligamentum teres. It was composed solely of vessels and did not contain parenchymatous tissue.

The umbilical vessels, the peritoneal sac, and the pedicle were ligatured and divided. The linea alba was closed completely and the stretched umbilical aperture of the skin lightly tied like the neck of a sack. Anaesthesia was not required because the operation was conducted through the umbilicus without incision of the skin. Signs of distress appeared only while the peritoneal sac was being treated. After 18 days a stitch abscess discharged, and after 4 weeks the umbilicus was firmly healed.

Macroscopically, the cut surface of the mass resembled liver tissue. This was confirmed by the microscope, which also revealed an early acute perihepatitis.

Discussion.

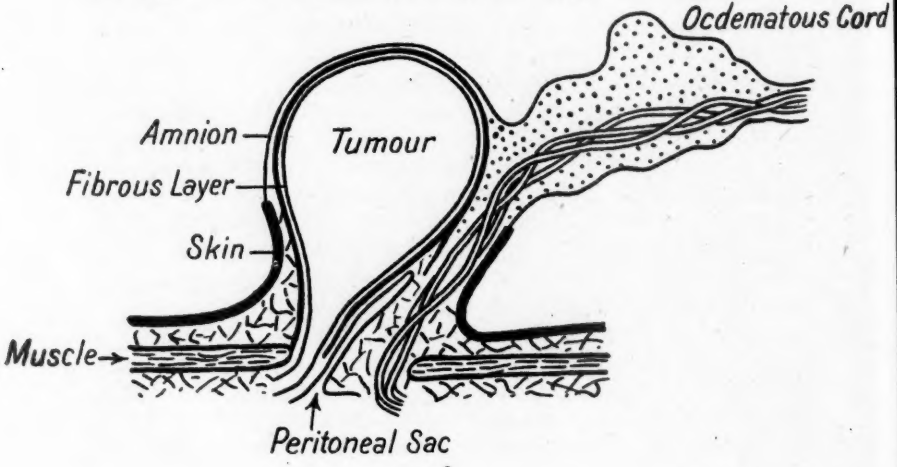
Consideration of the aetiology of the ectopia suggests two possible mechanisms. The condition bears a superficial resemblance to a partially healed umbilical hernia. That such healing may occur during intra-uterine life is shown by occasional cases in which a loop of intestine in a hernia is completely severed from the remaining intestine within the abdomen.

Against this theory the following arguments may be adduced. In the first place the liver is rarely or never found alone in a congenital umbilical hernia. The liver is, in fact, normally intra-abdominal during the whole course of development. Presumably in those cases in which liver is found in a hernia it has become eventrated into the sac persisting when the intestine has failed to return to the abdominal cavity. It is difficult to believe that after delay sufficient to allow herniation of the liver, the intestine should retreat and leave the liver stranded. Secondly, the mass of liver was not only extra-peritoneal, it was not even adherent to the outside of the fundus of the sac, although there was

a generalized fibrosis at the neck. It is unlikely that an organ developed between two layers of mesentery should lose all relation with peritoneum after becoming herniated. The continuation of the muscular layer over the liver mass as a fibrous sheet also weighs against the theory of healing umbilical hernia. In a true congenital umbilical hernia there is no such layer, because at the stage of development when the intestine prolapses the two halves of the abdominal wall have not fused in the midline.

The second and more probable hypothesis is that of an abnormality of growth. During the 2nd month the liver is proliferating rapidly between the layers of the ventral mesentery. It may be supposed that by an excess of growth this tissue might pass through the abdominal parietes pushing a layer of mesoderm ahead of it. Growth would be restricted at the level of exit, and a pedicle would develop. The path of least resistance would then be towards the umbilical cord, where expansion would be feebly though symmetrically resisted, thus giving rise to a pyriform tumour.

To call upon irregularities of growth processes is not to explain a congenital abnormality; it is to admit ignorance. The failure to realize this ignorance gives rise to many theories about mechanical and pressure effects in explanation of the various congenital abnormalities which are encountered. Although such mechanical theories may sometimes be correct, they are often without any foundation other than the lack of a better explanation. It is interesting to consider a case in which the findings resist a simple mechanistic aetiology.



A Case of Late Post-Partum Eclampsia

BY

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AND

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POST-PARTUM eclampsia occurring later than 48 hours after delivery is rare, and we think it worth while to place on record the following case.

The diagnosis of eclampsia (except when a post-mortem examination can be obtained) is made only by excluding other causes of coma or convulsions, and relying on certain signs and symptoms which should be present in the eclamptic woman. The most important of these are: the history of pre-eclamptic toxaemia in the preceding pregnancy or labour, the presence of albumin in the urine, a raised blood-pressure, and oedema. Although the blood-pressure was not greatly raised in the patient (120/90 immediately after the convulsion), the case fulfils these criteria in all other respects.

The convulsion occurred on the 16th day after delivery. In consulting the literature we find records of a number of cases in which the convulsion occurred later than the 2nd day, and the majority took place between the 2nd and the 16th day. Ivanyi[1] refers to 4 cases reported in the literature as occurring later than this (from the 24th to the 65th day), and Delmas-Marsalet and Dubarry[2] record a case of their own occurring on the 44th day. Some doubt is expressed by Tenney[3] as to whether these late cases should be classified as eclampsia, but Andérodias[4] suggests that since involution takes 3 months for completion the diagnosis of eclampsia in these late cases may be permitted.

CASE HISTORY.

Mrs. R.O., aged 24, a primigravida, presented herself at the antenatal clinic on November 20th, 1939. Her expected date of delivery was May 2nd, 1940, and she was seen regularly throughout pregnancy. Early vomiting was excessive but responded satisfactorily to in-patient treatment. A small amount of albumin was found in the urine only on one occasion (February 13th). The blood-pressure varied from 108/70 to 120/70. Oedema

first appeared on March 1st and was most marked in the vulva. The patient was readmitted for 3 weeks and the oedema subsided.

On April 9th she was admitted with premature rupture of the membranes. Marked oedema of the face and legs was present and there had been headache and vomiting for 24 hours. The blood-pressure was 134/90. Drug stimulation resulted in a normal delivery of a healthy child on the same afternoon. At 10 p.m. that evening the oedema was still very marked and the blood-pressure 196/120. Morphia was given and the patient placed in a single room to ensure a minimum of disturbance. The blood-pressure subsided rapidly and the oedema more slowly. On April 23rd the patient appeared quite well; there was no oedema and the blood-pressure was 120/70. She was discharged home.

On April 26th, 3 days after discharge, the patient collapsed in the street, and, from the description given by her husband, appeared to have had a typical eclamptic seizure. When seen in the receiving ward about an hour later she was just regaining consciousness and was confused. Headache was complained of, but there was no visual disturbance. Apart from two "giddy turns" prior to the fit there were no prodromal symptoms.

On examination there was slight oedema of her face and ankles. The blood-pressure was 120/90, and the urine contained a trace of albumin and sugar. The blood-count was normal and the blood-urea 54 mg. per cent. The retinae were normal. Potassium bromide and chloral hydrate gr. 10 of each was given on admission.

The patient's general condition improved rapidly. The urine was albumin-free on the 3rd day and the oedema had disappeared up by the 5th day. The blood-pressure varied little. She was discharged on May 3rd, and has remained well.

Our thanks are due to the Medical Superintendent of St. Giles' Hospital, S.E.5, and the Chief Medical Officer to the London County Council for permission to publish this case.

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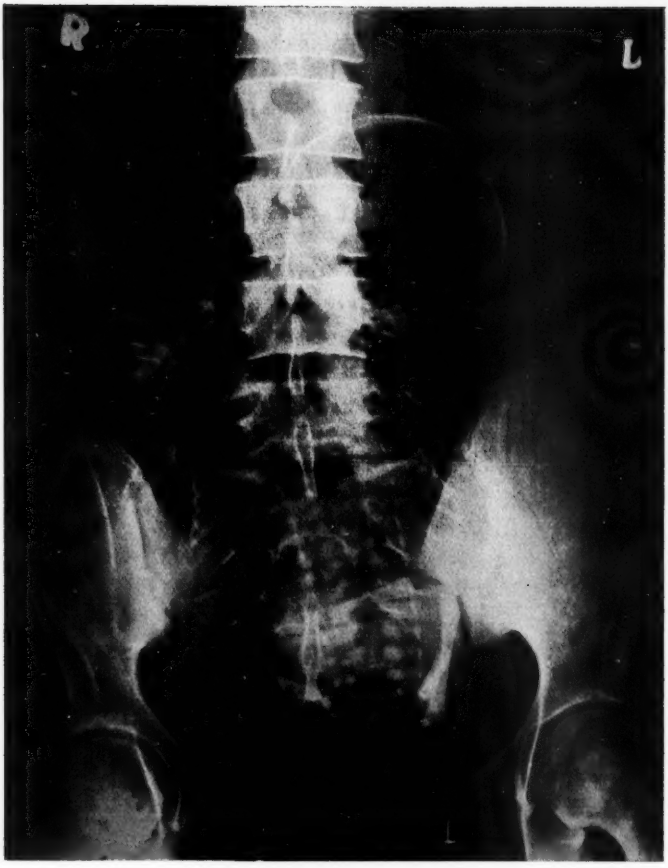

DICEPHALIC FOETUS

E.H.]

UNIV. OF MICH.

Diagnosis of Dicephalic Monster by Antenatal X-ray Examination

BY

ELIZABETH F. HUNTER, B.Sc. (Glas.), M.B. (Glas.), Ch.B. (Glas.), D.P.H. (Glas.),

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THE patient, aged 24 years, whose only previous pregnancy had terminated in abortion, was 7 months pregnant when she presented herself for the first time at the antenatal clinic on 29th September, 1939. The presentation was then a doubtful breech.

At a later examination, on 3rd November, 1939, the presentation was again doubtful, but there seemed definitely to be a head at the fundus. She was sent for an X-ray examination, and the report was as follows:

> "A very unusual appearance. There are two heads and two spines, but only two arms and two legs, one set of ribs and one pelvis, which is in the mother's pelvis."

Antenatal supervision in hospital was arranged, but, unfortunately, the patient went into labour prematurely, and was admitted as an emergency case.

The delivery, as a breech, of a female dicephalic monster, weighing 8 pounds, on 16th November, 1939, confirmed the diagnosis made by X-ray examination.

For the X-ray examination and report, and permission to use the X-ray plate reproduced, I am greatly indebted to Dr. Fergus Henderson, Ruchill Hospital.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The following have been elected to the Fellowship of the College :—

Armstrong, William Cunningham, Glasgow.
Edwards, Norman Llewellyn, Derby.
Gunn, Alistair Livingston, London.
Rose, John Kennedy, Edinburgh.
Taylor, Wentworth Alexander, Birmingham.
Watson, Robert, Northampton.

D.R.C.O.G., March 1941

The following have satisfied the examiners for the Diploma of the College : —

Calverley, Marie Hall, Manchester.
Cowan, Leonard Elliot, Bristol.
Dick, Ursula Marianne, London.
Dunster, Marjorie Olive, Bristol.
Foster, David Spencer, Sheffield.
Gordon, Ronald Rodger, Glasgow.
Gosse, Charles Noel, Cowley.
Howitt, Ruth Margaret, Epsom.
Jones, Iola Lloyd Trevor, Liverpool.
Milne, Agnes MacFarlane Duncan, London.
Overton, James, Leicester.
Rogerson, Mary Allen, Rochdale.
Sluming, Clarence Reginald, Liverpool.
Stacey, Christine Margaret, London.
Steed, Evelyn Elizabeth, Redhill.
Sutcliffe, Lucy Mary, Liverpool.

BOOK REVIEWS

"The Periodicity and Cause of Cancer, Leukaemia, and Allied Tumours: with Chapters on the Treatment." By J. H. DOUGLAS WEBSTER, M.D., F.R.C.P.E., F.F.R. Baillière, Tindall, and Cox. Price 12*s*. 6*d*.

THIS book is a thesis on one aspect of the cancer problem, and the author reviews the subject from the clinical, pathological, and therapeutical angles. The fact that recurrences of malignant disease tends to be noticed in phases has long been observed, particularly in cases of breast carcinoma with frequent waves of skin and bone metastases which appear, wax, and wane. Dr. Webster, from a study of some 800 cases of malignant disease of most common sites, has made a very interesting contribution. The book falls into two main sections: the first which deals with the clinical data, and inferences drawn from them would appear to be the more useful and convincing; the second which attempts to correlate the clinical findings with the virus theory of cancer does not carry conviction to the reader.

The activity of malignant disease according to the author's cases is phasic, and the times of maximal activity occur at intervals of 33 weeks, or multiples of fractions of this period. It is suggested, and the evidence seems reasonable, that observations of these periods in patients are of help in prognosis and treatment. Cases with a poor prognosis tend to have recurrences or increase in the size of the growth at half periods, whereas in cases with favourable prognosis periods may be missed and recurrence may then occur after multiples of 33 weeks. Moreover if this evidence of periodicity is accepted it is arguable that follow-up treatment should be based on the times when recurrence is likely, and possibly at these times, too, the growth should be more radio-sensitive. In trying to find factors which influence this periodicity it is suggested that it is more marked seasonally with a maximum occurrence between January and April. An adequate explanation of this cannot yet be given.

From this stimulating clinical essay the author proceeds to the deeper and more dangerous waters of theory. His findings are judged to be evidence for the virus theory of cancer, but the argument is not conclusive or detailed enough, based as it is on the similar periodicity of some of the virus diseases and the much disputed microscopic cellular anatomy of cancer cells. One feels that the author has here strained his slender thread too much, and would have been wiser to confine himself to his observations.

As a gynaecologist, having read this book, one feels that one should review our cases of cervical carcinoma in the light of Dr. Webster's evidence.

R. K. B.

"Recent Advances in Sex and Reproductive Physiology." By J. M. Robson, M.D., D.Sc. (Leeds), F.R.S.E., Lecturer in Pharmacology, University of Edinburgh. Second Edition. London: J. and A. Churchill, Ltd., 1940. 329 pages. Price 15*s*.

The difficulties facing the author of a book on recent advances in any subject, lie not so much in the actual writing as in assessing the degree of knowledge of his potential readers, and in choosing the aspects of his subject which are to be treated. In practice, advance in any field of scientific research is always proceeding along the whole front, though the speed of advance is by no means uniform. Consequently most books of this type consist of isolated essays on the most prominent topics, which plunge the reader straight into the midst of current research, sometimes with confusing effect.

In this respect Dr. Robson is fortunate. Practically the whole of our knowledge of sex and reproductive physiology may be classed as a recent advance, and it is possible to consider the whole field within the scope of a book such as this. In no way does this detract from Dr. Robson's very able achievement. Anyone familiar with such works as Allen's symposium, "Sex and Internal Secretions," will realize the vast amount of material that has to be sifted to produce a readable yet detailed view of the control and regulation of sexual and reproductive function.

The book is arranged logically, and starts with a consideration of the sexual cycle in the vagina and uterus, passing to a review of the biochemistry of the sex hormones and to a description of their various actions. Chapters are devoted to the influence of the pituitary gland, to the biological assay of the various hormones and their production and excretion, to ovulation and fertility in primates, to the maintenance of pregnancy and initiation of parturition, and to the mammary gland. All this part of the book is based on animal experimentation, and the author is careful to distinguish between the various types of test animals used, such as the rodent, rabbit, the bitch and the primate. It is only in the last, but longest, chapter that the clinical applications are dealt with, but this is reasonable since it is in sex endocrinology, above all other fields, that clinical progress has depended on experimental advances. It is only after a proper appreciation of the experimental work and the species differences that a rational human therapy can be instituted.

The book is generously illustrated with clear figures and photographs, and the references are sufficient for all important original work to be consulted without being so numerous as to interfere with the readability of the book. A minor blemish is the author's unabbreviated use of the phrase "*et alii*." Printed in full this appears rather pedantic, and is surely only justifiable if the right case is given; such phrases as "the results of Hamblen *et alii*" (p. 89), and "by Walsh *et alii*," (p. 118) strike a very curious note. Since the number of readers with a classical education is likely to decrease, it would seem desirable that such phrases should be printed

only in their abbreviated and anglicized form, but Dr. Robson's use of this particular expression must be wrong by any standard.

Details apart, Dr. Robson's book is undoubtedly the best introduction to the subject, and will be of great value both to clinicians and to potential research workers.

G. C. DODDS.

"Biochemistry of Disease." By MEYER BODANSKY, M.D., and OSCAR BODANSKY, M.D. The Macmillan Medical Monographs. New York: The Macmillan Company, 1940. 684 pages. Price 30s.

THE purpose of this book, according to the preface, is to guide clinicians in situations which call for the aid of biochemistry. As the authors rightly point out, most doctors learn what biochemistry they know in the first years of their training, before their clinical experience is sufficient for them to relate biochemistry to the treatment of disease. With the needs of the general practitioner in mind the book is, therefore, arranged in chapters each dealing with a separate class of disease, such as diseases of the blood, heart and the various endocrine organs. It is not intended for the laboratory worker, and routine biochemical tests are not described with the exception of those which the clinician might normally be expected to undertake.

Detailed accounts of treatment are not given, since it is assumed that the clinician has no need of guidance on this aspect. Thus, in the chapter entitled "Applications of Biochemistry to Problems in Obstetrics and Gynaecology," the causes underlying the disorders of the menopause are discussed, but no suggestion for treatment with oestrogens or mention of dosage is made. The new synthetic oestrogenic analogues are not discussed, despite their great practical and theoretical importance.

An attempt is made to deal with nutritional disorders in one chapter of 33 pages, and it is not surprising that there are some omissions. One would have thought, however, that most clinicians would have been glad of some information on the difficult question of vitamin E. While it must be conceded that the part played by this vitamin in combating sterility and abortion has yet to be proved, the problem is one of great interest to practising clinicians, and most would welcome a plain statement of current opinion on the subject. Mention of the important work done on the connexion between vitamin E and neuromuscular diseases is not made, although an entire chapter is devoted to diseases of muscle. Vitamin P is again not mentioned, but it is perhaps justifiable to consider that not sufficient work has been done on this vitamin for the clinician to know of it yet.

Nevertheless the book will be of great use to practising physicians who have no need of guidance to modern methods of treatment, but who wish to understand fully the biochemical basis of the disease they are treating. It is an expensive book, but to this limited class will no doubt be well worth possessing.

G. C. DODDS.

Review of Current Literature

Director: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the journals with which the "Journal of Obstetrics and Gynaecology of the British Empire" exchanges.

The Review of Current Literature has kept the readers of the Journal in touch with current literature throughout the world; owing to the war many journals with which the *Journal of Obstetrics and Gynaecology* previously exchanged are no longer received. At the end of the year an Index of all the subjects contained in the articles of the journals reviewed is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

J. LYLE CAMERON, F.R.C.S.; W. E. CROWTHER, M.B.; R. H. B. ADAMSON, M.D.; B. JEAFFRESON, F.R.C.S.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.; MEAVE KENNY, F.R.C.S.; JANE H. FILSHILL.

The Lancet

July 20th, 1940.

*Mothers under sixteen. Letitia Fairfield.

July 27th, 1940.

*Post-operative distension of the abdomen. Harold Dodd.

August 3rd, 1940.

Post-mortem Caesarean section with a living child. Joyce Morgan.
Induction of labour. (Leading article.)

August 10th, 1940.

*Excretion of pregnandiol in toxaemia of pregnancy. Cuthbert L. Cope.

MOTHERS UNDER SIXTEEN.

Because of the lack of accurate information concerning the pregnancy and confinement in young girls, Letitia Fairfield describes her findings in 74 such cases. These occurred between the years 1931 and 1938. Only one

of the girls was a certified mental defective and no other girl attracted notice as being probably defective. During the pregnancy, 9 of 68 patients, who had had antenatal care, showed a mild and transient toxaemia, and one had mild eclampsia. There was one case of ante-partum haemorrhage associated with the albuminuria; 5 patients had gonorrhoea but there was no case of syphilis. Premature labour occurred spontaneously in 8 cases between the 28th and 38th weeks; labour was surgically induced in 10 cases, 4 for disproportion and 6 for toxaemia. The full-time labours were surprisingly short and easy, but forceps were applied in 6 cases, probably to shorten the suffering of these child-mothers. Lacerations were no more common than in adult deliveries. In view of the theories advanced about the mental effect of childbearing on the very young, the author was unable to find any reference in the case-records of unusual anxiety, depression, or nervous instability during pregnancy, labour or the puerperium.

POST-OPERATIVE DISTENSION OF THE ABDOMEN: AETIOLOGY AND TREATMENT.

This complication is apt to occur, to a greater or lesser degree, following any intraperitoneal operation on the pelvic viscera. Dodd describes the two opinions held concerning the treatment: the active school which believes in remedies to restore the passage of flatus and faeces, and the rest school which aims at resting the alimentary canal and the entire patient until the exhaustion is overcome and the intestines resume function spontaneously. He remarks that a clear, concise, and consistently successful treatment is urgently needed, but he warns that it must not mask the clinical picture of acute intestinal obstruction. Under aetiology, he describes the local effect of trauma in and around the operation area, causing a regional leak of fluid into the intestinal wall, mesentery, etc., and the effect of constitutional factors of age, previous illness, the anaesthetic, pre-operative and post-operative management.

He stresses the importance of recognizing the sequence of events after every abdominal operation. For 36 to 48 hours the alimentary tract is inhibited, little or no flatus is passed, there is no gastric or intestinal activity, and the abdominal muscles are steadily guarded. This is followed by a similar period in which the alimentary tract resumes its function, but in an irregular spasmodic character, causing pain. These two vital processes last 72 to 96 hours and Dodd says that they must not be disturbed. He deplores the use of aperients, enemata, injections of intestinal stimulants or operative measures (A.E.I.O. and U. undertaker), but strongly recommends the resting form of treatment. On the day of excessive distension, nothing is given by mouth, but 120 ounces of fluid per diem is slowly injected intravenously, or better still subcutaneously, in the form of 5 per cent glucose saline. If there is no vomiting on the next day, flavoured drinks can be given by mouth to make a total daily fluid consumption of 120 ounces. Great care must be taken to chart the pulse-rate hourly, and the estimation of intake and output of fluid. No food or other fluids must be given until the pulse-rate falls to 72 to 74. If the patient has vomited twice, the stomach is washed out and kept empty by aspiration. Pain and discomfort are

relieved by the application of heat to the abdomen and the twin injection of morphine gr. ⅙ and coramine 1 c.c. four-hourly.

This paper gives many more smaller details of treatment and it should be read by all.

EXCRETION OF PREGNANDIOL IN TOXAEMIA OF PREGNANCY.

It has been confirmed that pregnandiol glucuronidate is the excretory end-product in the urine of progesterone. It is present in large amounts throughout the length of pregnancy, but in early pregnancy it can be made to disappear from the urine by the removal of the corpus luteum. This gland is the source of the hormone but this function is taken over by the placenta as the pregnancy progresses. Pregnandiol is also excreted in the urine in smaller amounts during the luteal phase of the menstrual cycle.

As it has been reported that the relatively large amounts of pregnandiol glucuronidate, which is present in the urine in normal pregnancy, is greatly diminished or entirely absent in toxaemia of pregnancy, the author investigated 10 cases of definite toxaemia to prove this statement. His findings were that in no case was the excretion very low, not even in a case of a woman suffering from eclampsia, and certainly it was never absent. In one case of chronic nephritis he failed to find any pregnandiol glucuronidate during the last week of the pregnancy. He thinks that renal damage is more likely to be the cause of interference with pregnandiol excretion than any real association with toxaemia.

BRYAN JEAFFRESON.

Nature

September 21st, 1940.

*Fat: an index of oestrogen and progestogen activity in the human endometrium.

FAT: AN INDEX OF OESTROGEN AND PROGESTOGEN ACTIVITY IN THE HUMAN ENDOMETRIUM.

The author, writing from the department of anatomy in the University of the Witwatersrand, Johannesburg, describes the remarkable shifts of sharlach R stainable fats in frozen sections of the human endometrium, and suggests that they may be routinely observed for diagnostic purposes.

In the oestrogen phase there is hardly any fat in the glandular epithelium; rarely, it is present in very small quantities in the supranuclear region. Fine droplets are found in the stromal cells, situated close to one or other pole of the nucleus.

In the late progestogen phase there is a remarkable accumulation of fat in the glandular epithelium, seen as fine red globules localized exclusively to the proximal third or half of the cell below the nucleus. The stromal cells contain very little fat at this stage.

On the first day of menstruation, the fat may extend throughout the

cytoplasm of the desquamating epithelium, with reduced quantities in the base of the surviving cells.

In very early pregnancy large amounts of this basal fat are found in the epithelial glands, and persist to the fourth or fifth month of gestation as large red globules in the cytoplasm of the flattened cells.

These agglomerations of fat in the epithelium can be induced by progesterone therapy.

The clinical value of these appearances may apply to those cases in which excessive and prolonged oestrogen production is suspected, and as a test for the presence of optimal quantities of progestogen.

Extended clinical trial of the reliability of this method of staining appears to be worth while.

M. KENNY.

The Australian and New Zealand Journal of Surgery

Vol. ix, No. 4, April 1940.

*The technique of panhysterectomy. F. A. Maguire.

THE TECHNIQUE OF PANHYSTERECTOMY.

Preliminary treatment to panhysterectomy for carcinoma cervicis should be devoted to removing fungating areas of the growth and clearing up local infection by surgical diathermy or by radium in the dose of 50 mgms. for 100 hours.

Catheterization is the first step in the operation; the vagina is painted with tincture of iodine and then packed with iodoform gauze. The abdomen is opened by an ample vertical incision and the lower edge of the parietal peritoneum is stitched to the lower angle of the incision. The ureters are recognized as they cross the pelvic brim immediately behind and in close relation to the ovario-pelvic fold. A traction suture through the fundus uteri is advised. The ovario-pelvic folds and round ligaments are ligatured and cut close to the pelvic brim. The appendages may now be removed so that the operation field is not obscured. The peritoneum of the utero-vesical pouch is divided and the cellular tissue between the broad ligaments exposed. The ureters are now isolated as they cross the pelvic brim and retracted inwards with the peritoneum to which they adhere. The internal iliac artery is exposed and the uterine branch dissected free from the ureter. The uterine artery is then divided between two ligatures, having been lifted clear of the ureter. Blunt dissection enables the ureter to be followed to the ureteric tunnel of Victor Bonney, and this band of connective tissue is cut through, protecting the ureter with the finger. The bladder and ureters are now pushed down off the vagina, and the utero-sacral ligaments clamped and cut. The paravaginal cellular tissue is next divided and the vaginal pack removed. The vagina is cut across after clamping the lateral margins. The angles of the vagina having been ligatured, the remainder of the vaginal incision is closed without drainage.

The final step in the operation is the dissection of the gland-bearing connective tissue at the brim of the pelvis and the lateral pelvic wall. After peritonization the abdomen is closed and deep retention sutures of silkworm gut are advised. T. N. A. JEFFCOATE.

American Journal of Obstetrics and Gynecology

Vol. xxxviii, No. 3.

*Studies on the concentrations of oestrogenic and gonadotropic hormones in the serum of pregnant women. A. E. Rakoff.

The growth of foetus and infant as related to mineral intake during pregnancy. W. W. Swanson and Vivian Iob.

The evaluation of the human vaginal smear in relation to the histology of the vaginal mucosa. Samuel H. Geist and Udall J. Salmon.

Changes in the uterine and placental circulations during different stages of pregnancy. P. J. Kearns.

The complications associated with excessive development of the human foetus. Arthur K. Koff and Edith L. Potter.

*The factor of anaesthesia in the pathogenesis of asphyxia neonatorum. Morris Rosenfeld and Franklin F. Snyder.

Certain laboratory findings and interpretations in eclampsia. L. C. Chesley.

B. Welchii infections in pregnancy. P. B. Russell, Jr., and M. J. Roach.

Prevention of tuberculosis begins before birth. Charles L. Ianne and James C. Muir.

Treatment of the menopause with oestradiol dipropionate. Edward M. Dorr and R. R. Greene.

*Surgical treatment of bilateral polycystic ovaries; amenorrhoea and sterility. Irving F. Stein and Melvin R. Cohen.

Family trends according to economic status. C. P. Sheldon.

Vitamin A deficiencies in pregnancy. W. A. Ricketts.

The changes of the urinary tract associated with prolapse of the uterus. A. J. Wallingford.

A study of a cause of hydramnios. J. R. Goodall, George Morgan, and R. H. Power.

Concentration of serum sulphate during pregnancy and in pre-eclamptic toxaemia. Arthur B. Hunt and E. G. Wakefield.

Concomitant ruptured ectopic pregnancy, hydrops of the gall bladder, and ovarian cyst. Fred H. Bowen.

A phenomenal single ovum twin pregnancy. John E. Hobbs and J. C. Jaudon.

Hydradenoma of the vulva. David Rothman and S. H. Gray.

Nephrectomy during pregnancy. G. L. Hoffman, Jr.

Ovarian pregnancy. E. W. Titus.

Carcinoma of the cervix in a girl of 19 years. H. Charache.

Specific urethritis in a male newborn. G. Wilson Hunter.
A simple technique for craniotomy on the high aftercoming head. G. W. Gustafson.
Dietary requirements in pregnancy. W. J. Dieckmann and W. W. Swanson.
The prevention of syphilis in marriage.
Review of new books.
Selected abstracts. Pregnancy and disease.

Vol. xxxviii, No. 4.

The metabolism and utilization of progesterone given intramuscularly to women. E. C. Hamblen, N. B. Powell and W. Kenneth Cuyler.
Toxaemia mortality in the Southern States. W. Z. Brandford.
Premature rupture of the membranes as a method of inducing labour. James R. McCord.
The relation of the time of ligation of the cord to the red blood-count of the infant. H. B. Frischkorn and M. Pierce Rucker.
Pelvic inlet variation in 400 negro women. Richard Torpin and L. P. Holmes.
Endometriosis of round ligament with report of case. John M. Fleming.
Current views on the causation of menstruation. Earl T. Engle.
The effect of ingested oestrone (progynon DH) and parenterally administered synthetic progestin (proluton) upon the human castrate uterus. Theodore Neustaedter.
*The anterior pituitary-like hormone in late pregnancy toxaemia. George van S. Smith and O. Watkins Smith.
The effect of crystalline corpus luteum hormone, progesterone, on the ovaries and related endocrine organs. Charles Mazer and S. Leon Israel.
The lipoid amnio-nitrogen in eclampsia and pre-eclampsia. Louis Hellman, Duncan E. Reid and Robert A. Moore.
The clinical significance of pelvic variations. Herbert Thoms, William R. Foote and Irving Friedman.
*Caudal anaesthesia in obstetrics. Arthur Baptisti, Jr.
The effect of pregnancy on gastric secretion. John S. Labate.
Rupture of pelvic inflammatory masses into the urinary bladder. Henry C. Falk and Samuel Hochman.
The uterus arcuatus. Frederick H. Falls.
Indirect external hysterography. Con Fenning, M. Edward Davis, and Fred L. Adair.
Prolapse of the uterus, hydronephrosis, hypertension. Paul H. Wosika and Chauncey C. Maher.
Relation of hydatid mole to habitual abortion. Francis E. O'Connor and J. S. Taylor.
Granulosa cell neoplasm with a discussion of possible histogenesis. Malcolm B. Dockerty and William C. MacCarty.
Immediate perineorrhaphy with knotless sutures. M. Pierce Rucker.
Suburethral abscesses, urine pockets and diverticula in the female urethra. Herbert E. Schmitz and Peter A. Nelson.

An unusually large tumour of the vulva. Alfred M. Hellman and Joseph Q. Jonas.

Vaginal removal of repeated ectopic pregnancy. Edward Allen.

Ruptured interstitial pregnancy after salpingo-oöphorectomy on the same side. Robert W. Bartlett.

Endometriosis of the round ligament simulating hernia. Arthur M. Dickinson.

Cavernous haemangioma of ovary in a girl 12 years of age. M. H. Schaeffer and J. James Cancelmo.

Apparent congenital absence of uterus. H. E. Bowles and C. M. Burgess.

An improved method for applying pelvic heat using air. Louis B. Newman.

Selected abstracts. Pregnancy and disease.

STUDIES ON THE CONCENTRATION OF OESTROGENIC AND GONADOTROPIC HORMONES IN THE SERUM OF PREGNANT WOMEN.

Because of the increasing evidence that a number of complications and abnormalities of pregnancy are associated with, if not actually related to, variations in the concentration of sex hormones in the body fluids, any method of estimating the concentration in the blood is of the utmost importance. In this paper Rakoff describes his technique for the estimation of oestrogenic and gonadotropic hormones and the importance of his findings in the diagnosis and treatment of abnormalities of pregnancy. He found that much more constant findings were obtained from blood-serum, rather than the 24-hour specimen of urine, in his preliminary tests, and therefore he felt that blood titrations would be more applicable to clinical use. He used unextracted sera in his tests and mice as the test animals; he was able to obtain reliable results with from 20 to 50 c.c. of blood, depending upon the period of gestation. He found that the oestrogen and prolan values on unextracted sera were much higher than those obtained on extracted specimens. In normal pregnancy the oestrogen value gradually rose as pregnancy progressed and reached its peak at term.

These findings are in accordance with the view that the oestrogenic hormones are formed by the placental tissue and that the larger amount present in the serum at term is needed to sensitize the uterus for the onset of labour. On the other hand, the prolan value was found to be greatest in the early weeks of pregnancy with its peak about the 12th week.

In 20 patients with toxaemia of late pregnancy he found abnormally high prolan and low oestrogen values. The patient with the highest rise in serum-prolan (1,800 M.U. per 100 c.c.) was admitted primarily because of marked oedema of the extremities and face and in one patient, in whom premature separation of the placenta occurred in a late case of pre-eclampsia, the serum-prolan was elevated to 1,000 M.U. per 100 c.c. while the serum oestrogen was unusually low at 66 M.U. per 100 c.c. In one case abnormally high values of serum-prolan preceded the clinical onset of toxaemia by 3 weeks. The authors also found that a continual fall of serum-prolan below the normal rate usually indicated death of the foetus.

THE FACTOR OF ANAESTHESIA IN THE PATHOGENESIS OF ASPHYXIA NEONATORUM.

Since it has been found experimentally that intra-uterine respiration of the foetus does take place, the problem of respiratory failure in the newborn has become more complex. This failure, then, must be regarded as being the suppression of a function which was previously active rather than the failure of a new mechanism to come into operation. In a previous paper these authors described three types of intra-uterine foetal apnoea, namely, acapulic, anoxaemic and anaesthetic. In this paper the authors give a description of the anaesthetic type. They describe how they performed their earliest experiments of observation of the rabbit's foetus through the uterine wall under general anaesthesia, how they did not recognize intra-uterine respiration until only the lightest anaesthesia was used, and how they were not able to appreciate the extent of these movements until general anaesthesia had been completely abolished. After these important observations had been fully grasped, the authors turned their attention to the effect of various types of general anaesthetics on the suppression of intra-uterine respiratory movement. The non-volatile group, pentobarbital sodium, paraldehyde, chloral, morphine, etc., when given intravenously, all markedly depressed or completely abolished respiratory movements, in doses well below those required to anaesthetize the mother.

A foetal apnoea of many hours' duration was thus obtained which was soon relieved by delivery of the foetus, although the respiratory movements remained partially inactive and sluggish and the foetus remained in a flaccid state for some time. Of the volatile group, they studied the effects of ether, nitrous oxide and cyclopropane. Under ether, regular foetal respiration could not be maintained at the level of surgical anaesthesia in the mother. After the elimination of the anaesthetic, foetal respiration often returned. The effect of nitrous oxide anaesthesia depended entirely upon the percentage of oxygen. Ten per cent of oxygen with 90 per cent of the gas caused rapid suppression of foetal respiration before the maternal animal showed evidence of anaesthesia; while 15 per cent of oxygen had no depressant action upon the foetus, even when administered continually for 40 minutes. On the other hand, cyclopropane had no depressant action on foetal respiration even when the mother was under deep surgical anaesthesia, and when delivered the foetus showed no signs of narcosis.

SURGICAL TREATMENT OF BILATERAL POLYCYSTIC OVARIES; AMENORRHOEA AND STERILITY.

For many years the authors have been interested in the disturbed ovarian-pituitary relation, resulting finally in amenorrhoea and sterility, associated with the presence of enlarged cystic ovaries. The enlarged ovaries were observed by the pneumoroentgenogram and were found to be 4 or 5 times larger than normal. They treated these cases by a wedge resection of each ovary and they report their results in a series of 28 cases, 7 of which had been reported previously. Microscopically, the most characteristic finding was the numerous follicular cysts. At first, they differentiated between

theca-lined and granulosa-lined cysts, but they now believe that this differentiation is of no significance. The theca cells as well as the granulosa cells are oestrin-producing, so the actual differentiation between such cysts was of no clinical importance. They also found a thick fibrous capsule which was often associated with increased fibrosis of the ovary and hyperplasia of the thecal layers. Although Robinson had reported that the presence of luteinization of the theca interna of atretic follicles was a characteristic finding in patients with metrorrhagia, the authors found it to be just as characteristic in their cases of amenorrhoea.

It is the belief of the authors that the presence of these cysts and the accompanying thickened tunica albuginea causes a mechanical obstruction to the development of deeper primordial follicles and consequent amenorrhoea and sterility. Therefore, they advise the removal of these cysts by a wedge resection and the suturing together of the cut edges. They do not advise leaving the raw area of the ovary open to the peritoneum or merely the puncturing of the cysts without resection. Of the 28 patients of their series, regular periods were restored in 23, irregular periods in 2, and in 3 cases there was no follow-up. In addition, 11 of 19 women, who were married, became pregnant, with a total of 15 pregnancies. During a follow-up of these cases no evidence of subsequent development of cystic ovaries was found.

THE ANTERIOR PITUITARY-LIKE HORMONE IN LATE PREGNANCY TOXAEMIA.

A series of 173 pregnant women have been investigated by the authors for a quantitative analysis of the anterior pituitary-like hormone in the serum. Their criteria for normal levels of this factor in pregnancy were based upon the analysis of 210 sera from 64 patients who were normally pregnant, and who continued so to delivery. A peak in the curve of this hormone, in both serum and urine, was observed at about the time of the second missed period and this high level was maintained for 1 to 3 weeks, a fact which gave an important means of differentiating between normal early pregnancy and a hydatidiform mole. By the beginning of the 4th month the hormone reached a constant low level which was maintained until delivery. Of these 173 cases, 85 were diagnosed clinically as pre-eclampsia or eclampsia and of these 75 (90.3 per cent) had a high estimation of this hormone in the serum. Eight other cases also had a high estimation and they all had a premature delivery between the 6th and 8th months. However, 5 similar cases of premature delivery had a normal quantity in the serum.

In order to find out whether the onset of toxaemia could be diagnosed by the serum examination before signs were recognized clinically, 82 patients were followed from the 5th month with repeated estimations at regular intervals. The authors found that in none of the 7 cases which were diagnosed as nephritic toxaemia or essential hypertension were the values at any time above the limits of normal. Of the 27 women who developed pre-eclampsia after the 7th month, 25 had an unmistakable rise in serum anterior pituitary-like hormone 4 to 6 weeks previously.

As the result of these and previous studies, the authors are of the opinion that the sequence of events leading to pre-eclampsia or eclampsia is as follows: (1) Excessive amounts of circulating anterior pituitary-like hormone, (2) a decrease of progestin and total oestrogen at a time when they normally increase, and (3) a striking change in the metabolism of oestrogen due to reduced progestin, this last abnormality being demonstrable at the time of the onset of clinically recognizable toxaemia.

To finish off this interesting paper the authors discuss the possible explanations of these abnormal quantitive hormone estimations in cases of pre-eclampsia, and they give their opinion that there is a failure of utilization of anterior pituitary-like hormone and its consequent excess in the serum. This excess can be used to diagnose an impending toxaemia many weeks before clinical signs appear.

CAUDAL ANAESTHESIA IN OBSTETRICS.

In this paper Baptisti describes his technique and experience of caudal anaesthesia for certain obstetric operations. The anaesthetic agent is deposited extradurally and acts on the nerve trunks in the space between the dura and the outer bony canal of the vertebral column. The injection is made through the terminal central sacral hiatus and the author claims that lower abdominal and pelvic anaesthesia can be obtained if a high caudal technique is employed or if the agent is injected with a moderate degree of pressure. His investigations suggest that 30 c.c. of 1 per cent novocaine with 8 minims of 1:1000 adrenalin solution through a 3½-inch 18 gauge spinal puncture needle gives the most reliable results. The needle is inserted with the patient in the knee-elbow position towards the canal, the opening of which can be felt as a horseshoe-shaped notch. After piercing a membraneous resistance nothing more is encountered until the needle has been inserted for about 2 inches. By lowering the hub of the needle the point can be felt to scrape along the overlying bone, which represents the anterior surface of the posterior sacral wall, for a total distance of 2½ to 3 inches.

The stylet is then withdrawn and if spinal fluid or blood is seen the injection should not be made without withdrawing the needle, until no fluid returns; 20 c.c. of the novocaine is then injected slowly and gently, and it usually flows with very little resistance. The extra 10 c.c. are injected if an anaesthesia higher than that of the perineum is needed. The patient is put flat on her back and in about 20 minutes anaesthesia appears around the anal region and ascends to a varying height. Labour pains become painless almost at once and they may become a little weaker, of shorter duration and less frequent for 5 or 10 minutes following the injection, but they soon return to their original status.

The author's opinion is that it is an excellent method for carrying the patient through the actual delivery and any necessary repairs. If the anaesthesia is administered in the first stage of labour, although painless contractions continue, the progress of labour will probably be assisted until the anaesthesia wears off. In his series of 200 cases he was unable to enter the sacral canal in 14 and these are classified as complete failures. As most

of these occurred in the first 50 cases it shows that experience plays a most important part, although Baptisti is sure that there is an irreduceable minimum of failures when the patient is too obese or when there is an abnormal sacral contour. In 4 other cases the canal was entered but the anaesthesia was absent or only partially present. In the remaining 182 cases, the anaesthesia was classified as successful although in 17 cases some form of supplementary anaesthesia had to be given. These occurred again in the early part of the series and the author thinks that it was due to the operation being started too soon.

The advantages claimed for this method are that the anaesthesia is complete, the uterine contractions become painless and that the perineum is markedly relaxed. Also, the patient can still co-operate by bearing down voluntarily and blood-loss is reduced to the minimum.

BRYAN JEAFFRESON.

The Journal of the American Medical Association

Vol. cxv, No. 1, July 6th, 1940.

*The treatment of hypoprothrombinaemia haemorrhagica neonatorum with vitamin K. H. G. Poncher and K. Kato.

Vol. cxv, No. 2, July 13th, 1940.

*A micro bedside test for the determination of the sulphanilamido group concentration in body fluids. E. W. Schoeffel.

Vol. cxv, No. 4, July 27th, 1940.

*Cyclic pulmonary oedema at menses in mitral stenosis. J. Edeiken and J. Q. Griffith, Jr.

Vol. cxv, No. 7, August 17th, 1940.

*Vulval fusion. M. F. Campbell.

*Endometriosis of the ileum with chronic intestinal obstruction. P. M. Glenn and J. J. Thornton.

Vol. cxv, No. 10, September 7th, 1940.

*Sulphathiazole. W. Spink and H. Hansen.

Vol. cxv, No. 12, September 21st, 1940.

*Foetal and neonatal deaths. Edith A. Potter.

THE TREATMENT OF HYPOPROTHROMBINAEMIA HAEMORRHAGICA NEONATORUM WITH VITAMIN K.

A total of 22 cases of haemorrhagic disease of the newborn forms the basis of the present report. In all these cases the prothrombin clotting time was determined by the micro method of Kato, both before and after the institution of vitamin K therapy.

The frequency of clinical forms of bleeding in the present series was as follows: haematemesis, 16 cases; melaena, 8 cases; omphallorrhagia, 8 cases; dermal or cutaneous haemorrhage, 3 cases; cerebral symptoms 3 cases and haematuria, 2 cases. In the majority of instances two or three of these symptoms occurred in the same case.

The average prothrombin clotting time in 10 cases before treatment was 210 seconds, the shortest being 110 seconds and the longest 272 seconds. In 12 cases before the institution of vitamin therapy the prothrombin time was prolonged beyond 5 minutes.

The average prothrombin time for all cases during the 24 hours following treatment was reduced to 26 seconds. In most of the cases, shortening of the prothrombin time could be demonstrated within from 2 to 6 hours after the administration of antihaemorrhagic vitamin.

The preparations of vitamin K used in our series were (1) 2 methyl-1, 4 naphthoquinone (vitamin K_3); (2) 2 methyl-4, amino naphthol hydrochloride (vitamin K_5); and (3) solution of 2 methyl-1, 4 naphthoquinone in sodium bisulphite. The fat-soluble preparation, 1, was administered by mouth, and the water-soluble preparations, 2 and 3, were given intramuscularly and subcutaneously. While water-soluble preparations can be effectively given intravenously, the most accessible routes of administration were purposely chosen for practical reasons.

Neither intravenous nor intramuscular blood was used, since in none of the cases did any sign of severe post-haemorrhagic anaemia develop.

In a recent study of 173 newborn infants it was found that the average prothrombin time on the first day of life, as determined by the micro method, was 43.2 seconds for the normal mature infants and 46.5 seconds for the premature infants. These values decreased with the growth of the infants, so that by the 6th to the 10th day of life the majority of the infants showed the average normal prothrombin time of approximately 25 seconds.

It must be emphasized that, in order to treat hypoprothrombinaemia in the newborn effectively, an early and correct diagnosis is imperative. In this connexion a grouping of hypoprothrombinaemia in the newborn into clinical and subclinical types is suggested. It is indisputable that both forms of hypoprothrombinaemia are due to vitamin K deficiency, differing only in degree of such deficiency; hence the specific therapy required is identical in the two groups.

Clinical improvement was both prompt and permanent with all preparations tested.

From these observations it may be concluded that vitamin K and its esters are specific in the treatment of hypoprothrombinaemia haemorrhagica neonatorum.

A Micro Bedside Test for the Determination of the Sulphanilamido Group Concentration in Body Fluids.

Schoeffel gives a detailed description of the technique for the clinical determination of the concentration of the sulphanilamido group in the blood. Marshall's method together with the spot test filter paper method form

the principal means by which this rapid test is accomplished. It is fitted for determination of the drug concentration in the blood, without the aid of laboratory facilities, by the physician or his technician at the bedside even in rural districts.

Cyclic Pulmonary Oedema at Menses in Mitral Stenosis.

Cyclic pulmonary oedema was observed during 14 successive menstrual periods in a young woman with advanced mitral stenosis. Mercupurin given intravenously during an attack prevented further attacks during that menstrual period. The attacks were presumed to be due to retention of sodium chloride and water in the blood, possibly due to the increased excretion of oestrogens or progesterone in the urine, possibly because of disturbed posterior pituitary activity at the menses. The patient showed an increased blood-volume on the first day of one of the periods and the serum contained an antidiuretic substance for rats and a melanophore expanding substance for frogs. Following irradiation of the posterior pituitary with 1,132 Röntgen units in 8 doses, the patient became free from her attacks until she died 10 months later of mesenteric thrombosis and fibrillation. Six months after the irradiation the serum contained no antidiuretic substance, but the melanophore expansion test remained positive. The last attack may have been attributable to a rather hilarious party which the mother says she went to, the night before the period came on, a factor which may have complicated the scientific aspects of the case.

Vulval Fusion.

The author has seen 9 instances of vulval fusion, all brought to him before puberty as cases of pseudohermaphroditism. In a typical case the vulva presents a smooth, reddish, mucosal surface extending forwards and usually covering the clitoris. With the labia majora separated, the vulva appears all perineum up to the subpubic level. Below the clitoris there is a small orifice through which urine is passed. In every case there was an associated urinary infection. Rapid cure followed division of the adhesions. The pathology of the condition is discussed.

Endometriosis of the Ileum with Chronic Intestinal Obstruction.

Two cases of ileal endometriosis producing chronic intestinal obstruction are described. In one case the symptoms were worse at the menstrual periods. The lesions were in the terminal part of the ileum. Microscopically endometrial islets were found scattered throughout the muscularis with fibrosis and focal lymphocytic infiltration of the muscularis and serosa. The obstruction was due to the productive fibrosis and not to the tumours themselves. The appendages were found buried in adhesions. Satisfactory recoveries were obtained after resection of the affected segment and ileo-caecostomy. The pre-operative use of a Miller-Abbott intestinal tube was valuable in controlling the obstructive symptoms both before and after operation, and also in localising accurately the point of obstruction.

SULPHATHIAZOLE.

The literature is reviewed and the results obtained with sulphathiazole in 128 cases are described.

In 33 cases of pneumococcal pneumonia sulphathiazole appeared as effective as sulphapyridine. One of 3 patients suffering from pneumococcal meningitis recovered with sulphathiazole and type specific serum.

Fifteen consecutive patients with staphylococcal septicaemia were successfully treated. One patient subsequently died of leukaemia.

The results of the use of the drug in 20 cases of urinary tract infection suggest the drug may be a useful adjunct to therapy, particularly in staphylococcal, *b.* proteus and alpha haemolytic streptococcal infections.

The drug was readily absorbed and quickly excreted in the urine, while the degree of conjugation observed was less than that occurring with sulphapyridine, the average amount fixed in the blood being only 20 per cent. Less nausea and vomiting were noted as compared with sulphapyridine, but dermatitis was more frequently encountered with sulphathiazole than with either sulphanilamide or sulphapyridine.

FOETAL AND NEONATAL DEATHS.

This is a report of 2,000 autopsies on stillborn foetûs and infants dying within 1 month of birth. The material was classified in 5 ways: time of death in relation to birth, gestational age at birth, method of delivery, complications of pregnancy and labour, pathological changes found.

The foetus died before labour in 32 per cent of the cases, during labour in 28 per cent and after birth in 40 per cent. Of the 795 neonatal deaths 70 per cent occurred within the first 48 hours of life. The results suggest that the factor of immaturity may be more of a hazard in the neonatal phase than during the passage of the foetus through the birth canal.

No pathological findings were noted in 43.5 per cent of the total autopsies and in most of these cases the actual cause of foetal death was to be sought in the maternal conditions which incited the onset of labour. Evidence of asphyxia was the commonest lesion observed, 19.4 per cent, and next was traumatic haemorrhage, 14.3 per cent. The results indicated that the mature infant has twice the likelihood of succumbing to mechanical injury and haemorrhage as the premature infant. Most of the injuries were cerebral. It is interesting to note the only cerebral lesion found in the premature group was intraventricular haemorrhage (24 cases). Malformations were the cause of death in 10 per cent of the whole group.

The only infection of any pregnancy was pneumonia. In a few cases the pneumonia developed during the course of labour. The incidence of pneumonia as a cause of death increased with each day of extra-uterine life. In addition to the 7.9 per cent of deaths directly due to this cause, pneumonia was found in a smaller proportion, 3.7 per cent, as a complication of some other lesion such as intracranial haemorrhage.

In the final analysis the author stresses the fact that in about one-quarter of the total cases no known factors were present in the maternal history which might reasonably have been expected to contribute to the fatal out-

come, and no abnormalities were found in the foetûs. This group of foetal deaths without apparent cause is a large one and constitutes one of the most baffling problems in obstetrics, a problem urgently in need of investigation.

Correlation with maternal age was possible in 1,881 cases. A lower incidence of foetal and neonatal deaths was found in the mothers under 30, and a higher incidence in the group over 30 than would be expected if the deaths were distributed evenly at all ages in proportion to births. Prematurity, however, without evident cause was commoner in the younger group of mothers.

Surgery, Gynecology and Obstetrics

(With international abstract of surgery.)

Vol. lxxi, No. 2, August 1940.

Observations on the Roentgenological evidence of foetal death. H. Thoms.

Cancer and its relation to pregnancy and delivery, to marital and social status. S. Peller.

*Causes of death in cancer of the cervix uteri. L. Austen and A. Sala.

Causes of Death in Cancer of the Cervix Uteri.

These authors have analysed 124 cases of cancer of the cervix uteri, upon which autopsy was performed, in a ten-year period. The analysis was carried out to illustrate the conviction that, with few exceptions, patients harbouring malignant neoplasms do not die directly as a result of their cancers, but of secondary pathological manifestations initiated by the disease or its treatment.

Unless such secondary effects occur, the patient may live in relative comfort for many years.

It is shown by the authors that the average duration of life is about 17 months. Approximately equal numbers of these women had sought treatment in the early, later or very late months after the appearance of the first symptom, which in nearly 90 per cent of cases was vaginal bleeding, but almost 80 per cent were in a markedly advanced stage of the disease when first examined. This fact is borne out by personal experience in populations of like indigence and indifference to personal hygiene, and indicates the necessity for educational measures designed to emphasise an appreciation of the significance of vaginal discharge or bleeding.

Thirty-seven cases at autopsy had vesico-vaginal or recto-vaginal fistulae, often multiple, and thought to be the indirect result of operative trauma, radium or X-ray treatment, and not of neoplastic invasion by direct continuity. These sped the progress to death by assisting urinary and peritoneal sepsis.

Indeed, local sepsis was found to be the primary cause of death in 13 per cent of cases. Peritonitis carried off 14 per cent and was usually due

to pyometra with perforation of the uterus. Interference with uterine drainage is the basic factor and is found almost as often in cases in which the cervical lesion is controlled, or even healed, as in those in which drainage is blocked by bulky tumefaction.

Twenty-two per cent died of generalized sepsis, but the largest group, 25 per cent, had the major infective lesion in the urinary tract due to interference with drainage. Gynaecologists are often concerned to know whether urological operations designed to improve drainage should be carried out to prolong life in patients in whom the cancer has been apparently checked by surgery or irradiation. It is thought by these authors that these operations are rarely helpful, as their autopsy studies show, almost consistently, that obstructive lesions are the result of neoplastic invasion and not of fibrosis following an extensive exposure to radium or deep X-rays.

Haemorrhage and anaemia in 8 per cent, and pneumonia in 5 per cent of cases only, were thought to account primarily for death, although both play an important secondary rôle in a larger number, especially pneumonia.

In only 4 per cent of all cases was death considered to be directly attributable to distant dissemination, these being instances in which the lungs, heart, or mediastinum were involved. Skeletal metastases occurred in only 8 cases.

Only 3 patients died of cardiac failure, one of intestinal ileus and one of pulmonary embolism.

This careful review excludes cachexia as a clinical diagnosis. No cancer toxin poisoning the system need be postulated to explain why unchecked cancer ultimately kills. Carcinoma of the cervix kills by mechanically interfering with the physiological function of organs in its neighbourhood.

M. KENNY.

American Journal of Diseases of Children

June, 1940.

*Imperforate hymen causing hydrocolpos, hydroureter, hydronephrosis and pyuria. C. Kereszturi.

IMPERFORATE HYMEN CAUSING HYDROCOLPOS, HYDROURETER, HYDRONEPHROSIS AND PYURIA.

The author reports a case of completely imperforate hymen in an infant causing retention of vaginal secretions and the formation of a hydrocolpos by the sixth week of life. The resulting pelvic tumour attained sufficient size to cause displacement of the colon and pressure symptoms of the rectum. Intermittent retention of urine led to hydroureter and hydronephrosis, gross infection of the urinary tract and severe illness. Recognition of the cause of all these symptoms came only after useless laparotomy, and even after incision of the hymen was performed, complete recovery was delayed for

many months and complicated by pyocolpos when the infant was nearly 2 years old.

Review of the literature shows 54 reported cases of imperforate hymen causing symptoms before puberty, the ages ranging from birth to 7 years. The vaginal contents released by incision of the hymen vary remarkably in the different cases, and it is probable that in the instances in which purulent infected material was drained, the hymen was not entirely imperforate and organisms were able to gain admittance to the vagina. In the majority of cases in which the hymen is abnormally thick and completely imperforate, the vaginal contents are sterile and consist in mucous and squamous epithelial cells. The infants usually do well after operation. The importance of this uncommon condition lies in the fact that the diagnosis may be overlooked and abdominal operative procedures undertaken to the risk of the baby's life. It is interesting to note that none of the reported cases had haematocolpos, although transient vaginal bleeding is a far from rare occurrence in the newborn.

M. KENNY.

American Journal of Roentgenology

1940, No. 43.

*Radium treatment of carcinoma of the cervical stump. R. E. Fricke and H. H. Bowing.

RADIUM TREATMENT OF CARCINOMA OF THE CERVICAL STUMP.

The authors show that carcinoma of the cervical stump occurs most often at the time of the menopause and after subtotal hysterectomy for uterine fibromyomata. The lesions when discovered are most often in an advanced stage and the prognosis is poor. They suggest that when uterine myomata are known to be present in cases of vaginal bleeding, investigation of causes of the bleeding other than the myomata should be carefully performed or a coincidental early cancer of the cervix may be overlooked.

When the removal of the uterus is necessary, the decision to perform subtotal or total hysterectomy would be easier for surgeons if the true incidence of stump cancers was known more clearly. But it is very difficult to determine, and is probably higher than the follow-up of cases by gynaecological clinics suggests. Radiological clinics, in the treatment of carcinoma of the cervix, have found a far higher incidence of malignancy in the retained stump than have gynaecological clinics. In 15 years' experience at the Mayo Clinic, the incidence of stump carcinoma to all cases of carcinoma of the cervix was about 1 in 15. This high figure should, however, be pruned. If the carcinoma is not discovered until two years or longer have elapsed since the subtotal hysterectomy, the lesion is probably a true carcinoma of the stump, and not a coincident malignant lesion present when the operation was performed. Cure for five years was obtained in 26 per cent of the cases by improved radium and X-ray therapy,

although 80 per cent of cases were in stages 3 and 4. But, as with incomplete operations for carcinoma anywhere in the body, the results were not so fortunate in the coincident cases, those discovered less than two years after the subtotal hysterectomy and probably existing at the time of the operation. More than half of this group died within the first year after treatment (compared with only 23 per cent of the patients in which true carcinoma had developed) and the lesions were more advanced when first seen. A strong case is made for a conscientious examination of the cervix whenever subtotal hysterectomy is performed; the patient should have pelvic examinations at regular intervals thereafter, and should be instructed in the importance of reporting the occurrence of vaginal bleeding or discharge.

M. KENNY.

Annali di Ostetricia E Ginecologia

Vol. xviii, No. 1, January 1940.

An account of work done by the gynaecological section of the Victor Emanuel III Institute in 10 years for the cure of tumours. Natale.

*Macroscopic and microscopic anatomy of the foetal uterus. Matteace.

*Plastic operations for complete inversion of the bladder due to dystocia. Colombino.

Lipoid content of the uterine mucosa. *Note I*: Research on the lipoid content of the uterine mucosa in various periods of the menstrual cycle. Zambelli.

Mammary function of the newly born in relation to their endocrine state. Micheloni.

Vol. xviii, No. 2, February 1940.

*Late recurrence of carcinoma of the uterine cervix. Silva.

*The ambo-sexual nature of genital hormones: experimental research on the uterus, ovary and hypophysis of the rabbit. Giuffrida.

Clinical investigation of ovarian function after partially destructive operations on the genital system. Pugliatti.

Polipeptidaemia and polipeptiduria in obstetrics and gynaecology. *Note III*: In normal and pathological puerperal conditions. Montanaria and Nicoletti.

*Folliculinuria and folliculin-therapy in the toxaemias of pregnancy. Borsetti.

Vol. xviii, No. 3, March 1940.

*Macroscopic and microscopic anatomy of the uterus of the newly born infant and of the child before puberty. Matteace.

A case of a mongoloid dwarf and pregnancy. Bertino.

Clinical notes on some cases of perforation of the uterus. Salvini.

Pathological torsion of the uterine adnexa. Tamcurello.

Activity of protective ferments. *Note III*: Action of certain reducing substances on Aberhalden's pregnancy reaction. Mariani and Mingazzini.

THE MACROSCOPIC AND MICROSCOPIC ANATOMY OF THE FOETAL UTERUS.

Matteace publishes personal observations of foetal uterine development gained from sections taken from the 3rd month onward to the 9th. He pays special regard to the epoch of fusion of the Müllerian ducts, the signs of distinction between the portio, vagina and segments of the uterus, and the first appearance of muscular and elastic tissue, glands and blood-vessels in the uterine walls.

Macroscopic anatomy. In the 3rd month the vaginal tract cannot be distinguished from the uterine, the portio is only a circle in the lumen of the tract, the mucous folds mere traces in its walls. In the 5th month the uterine tract can easily be distinguished from the vaginal, and shows division into its segments. In the 6th and 7th months there appears progressive development of the segments and elongation of the cervical canal. Often the uterine cavity is full of mucus. Between the 4th and the 9th months blood-vessels are formed in the uterus and vagina. The 5th month shows the first development of glands.

Microscopic anatomy. On the microscopic side he follows, and illustrates by microphotographs, the development and changes in the epithelium—e.g., from columnar to stratified epithelium in the portio and cervical canal, the appearance of blood-vessels with characteristic elastic and muscular fibres in their walls, of mucous papillae, and of glands which become racemose in the cervix and tubular in the fundus.

In all his sections, he has noted only one case of congenital erosion of the portio and 3 of ectropion, all in foetal uteri between the 8th and the 9th months. The opposite anomaly, penetration of the cervical canal by the pavement epithelium of the portio, is more frequent. These atypical forms of epithelium investiture may be interpreted as phases of uncertain reaction to progressive development of the genital canal.

PLASTIC OPERATIONS FOR COMPLETE INVERSION OF THE BLADDER DUE TO DYSTOCIC PARTURITION.

Colombino describes treatment of a case in which great destruction of the lower genito-urinary canal had been caused by extensive necrosis of tissue after dystocia.

The history given by the patient, who was aged 33 and had had 3 children, was that her first two deliveries had been instrumental but without after-disturbance. The 3rd was also instrumental, followed by a long feverish illness with involuntary loss of urine. She had remained in bed in hospital for 5 months and had undergone 2 operations for incontinence of urine, before admission to the author's hospital in Milan.

Examination there showed that the vaginal fornices were partially

annulled, the anterior wall, the trigone, the urethra, and the urogenital diaphragm no longer existed. Through the great cavity thus formed protruded a completely inverted and prolapsed bladder adherent to part of the cervix. The uterine body was normal in size. After 4 consecutive operations in about a year's time, he obtained sufficient anatomical reconstruction and relative continence, chiefly by interposition of the uterine body below the pubis.

The first task of replacing the herniated viscera was comparatively easy. His second aim of producing sufficient capacity and relative continence in the bladder was much more arduous. Variants of Martius's operation were only partially successful, since the urethra constructed between the fundus and the pubis symphysis served only as a canal for drainage. Another canal had to be formed across the uterine isthmus. Implantation of the ureters into the large intestine was not attempted for fear of septic complications.

Late Recurrence of Carcinoma of the Uterine Cervix.

Delayed recurrence of cervical cancer occurs in only about 2 per cent of the total number of cases reported as completely cured, 5 years after removal of the original tumour.

The frequency of late recurrence seems to be independent of the histological nature and degree of development of the primary tumour, and of the manner of cure, whether surgical or radiological. This behaviour, differing considerably from recurrence within 5 years' interval, suggests that a constitutional resistance has been acquired to neoplastic development.

Silva describes a case observed in a patient who had a glandular carcinoma of the cervix. The diagnosis was based on both clinical and histological evidence, and endocervical treatment with radium was given till the tumour disappeared.

Examined periodically for 5 years at the Cancer Institute, a definite cure was reported at the end of that time. Two and a half years later in apparently good health a large abdominal mass developed.

Laparotomy was performed, and an adenocarcinoma, which filled and distended the fundus uteri, was removed surgically and successfully. The tumour was of the same histological type as the one removed 8 years previously from the cervical wall.

The interest of the case lies in its rarity, its slow evolution, and in important deductions which might be drawn as to treatment.

The Ambo-sexual Character of Genital Hormones: Experimental Research on Uterus, Ovary, and Hypophysis of the Rabbit.

From experimental research on the rabbit with propionate of testosterone, Giuffrida has obtained results which indicate the ambo-sexual character of this hormone. Indeed, the modifications which occur in the

uterus, ovary, and hypophysis after injections of testosterone are strictly analogous to those which follow the administration of folliculin or progesterone.

He asks the question whether the typical female hormone folliculin is exclusively derived from the ovary, since a greater quantity of folliculin is eliminated in the menopause, after bilateral oöphorectomy, and even in advanced age. If the distinctive sex hormones, male and female, do not exist separately in the organism and can be isolated when chemically prepared by synthesis, how can it be said that male and female sex hormones are antagonistic? It might be better to term their relation "convergent synergism," developing in the cross-path of the hypophysis. Clinically it has been observed that cases of functional metrorrhagia end by reacting favourably to either folliculin, luteal hormone, or recently to testosterone. From the clinical point of view, the beneficial therapeutic action of testosterone may find explanation in the fact that its ambosexual nature renders it in some cases equally efficacious to folliculin or progesterone.

FOLLICULINURIA AND FOLLICULO-THERAPY IN THE TOXAEMIAS OF PREGNANCY.

Borsetti briefly reviews various hypotheses which have been formed from time to time regarding the complex pathogenesis of gravid toxaemias. The earliest concerned nervous disturbance, mechanical pressure, hepatic and renal toxins. Recent research has taken a new direction founded chiefly on chemical examinations. Langemeister demonstrated that in eclampsia there was an increase of ammoniacal urine and a decrease in alkalinity of the blood. Hoffman and Opitz pointed out that there was also a blood deficiency of calcium salts.

McIlroy and other English obstetricians believe that gravid toxaemias are largely due to congenitally vitiated metabolism, and that a diet rich not only in salts of calcium and iodine but in vitamins A, B and C, will prevent and cure the pre-eclamptic state.

The latest theory in order of time is the hormonic, based on the excretion of folliculin and prolan. In gravid toxaemias the curves of elimination of these are distinctly inverse to the normal, prolan is increased and folliculin diminished. Careful study of hormonic research has led Borsetti to conclude that a pathogenetic relation between folliculin deficiency and eclampsia is the most plausible explanation of gravid toxaemia.

On this basis, he has successfully treated and prevented recurrence of eclampsia in a patient, pregnant for the third time, whose two previous pregnancies had been marked by severe eclamptic attacks followed by stillbirths. In accordance with data from Smith, Luisi and Alfieri, injections of folliculin (crystallovar) were given in small and continuous doses from the fourth month onward. Subsidiary aids of rest and diet were not neglected. Pregnancy ran a normal course ending in the birth of a live and healthy child.

MACROSCOPIC AND MICROSCOPIC ANATOMY OF THE UTERUS OF THE NEWLY-BORN INFANT AND OF THE CHILD BEFORE PUBERTY.

Matteace follows his study of foetal uterine anatomy (January 1940) by describing post-natal uterine development from birth to puberty. Unlike prenatal evolution, this is not continuously progressive, but, as his graphs illustrate, there are sudden advances with short periods of rest. Immediately after birth there begins a rapid process of regression for all the uterine tissues, "the post-foetal involutionary crisis." The fundus shows a greater degree of involution than the cervix, appearing in some cases like an appendix to the cervix. The threshold of involution is reached about the 2nd year. Development then proceeds gradually up to the 10th year, when a graph shows a rapid ascent becoming remarkably steeper just before puberty. This epoch coincides with physical transformations such as enlargement of the breasts, recognized as secondary sexual characteristics. Anomalies of morphology and epithelial investiture of the portio sometimes occur, and may persist exceptionally in the virgin, giving rise to congenital erosions.

J. H. FILSHILL.

La Ginecologia

Vol. xviii, No. 1, January 1940.

*Radiology in female sterility. Robecchi.

Vol. xviii, No. 2, February 1940.

The behaviour of peripheral and medullary blood in the puerperium. Giuffrida and Borghese.

*Local anaesthesia in obstetric vaginal operations. Sannicandro.

*Obstetric findings in some cases of osteoporosis. Ponzi.

*First observations on the clinico-therapeutic value of a new oestrogen preparation—diethyldiossistilbene. Lorenzetti.

Vol. xviii, No. 3, March 1940.

The aetiology and real therapeutic basis of human sterility. Berutti.

*The control of the biological activity of female hormones. Torboli and Ferrari.

RADIOLOGY IN FEMALE STERILITY.

Robecchi considers radiological examination and treatment to be of indispensable value in gynaecological cases. During the last 15 years, intrauterine injections of substances of contrast and hystero-salpingographic examination have shown that only half the cases of female sterility recorded were due to tubal occlusion; either functional or anatomical, judging by frequencies of pregnancies which occurred after hystero-salpingography and appropriate treatment; he considers it a method which

merits extended use. He thinks its risks, such as inflammatory reaction in tubes, ovaries, peritoneum, blood-vessels or lymphatics, have been much exaggerated and are often transient and of secondary importance.

In cases of irregular menstruation he has found that irradiation of ovary, hypophysis, thyroid or thymus has been of subsequent value. His results are confirmed by literature on the subject.

Local Anaesthesia in Vaginal Obstetric Operations.

Sannicandro describes and illustrates by diagrams local anaesthesia of pudendal nerve filaments which lie under the levatores ani muscles in the ischio-rectal fossa, in the peri-anal zone, the anterior part of the perineum, the labia majora and the labia minora.

In his own experience, he found one injection into the perineum sufficient. He used a 2 per cent solution of novocaine without adrenalin.

It is a method which finds many indications in vaginal obstetric operations such as colpoperineorrhaphy, episiotomy, high and low forceps extractions, and in foot presentations especially in primiparae. This is particularly true in cardiac or renal cases in which a general anaesthetic might be dangerous. There are many advantages in the method and almost no risk if care be taken as regards the wounding of blood-vessels. It is worthy of more extended employment especially in cases which must be treated at home.

Obstetric Lesions in some cases of Osteoporosis.

The disease *osteoporosis* or the *syndrome of the blue sclerotic*, fairly well known to ophthalmologists as of typical Mendelian heredity, was described clearly by Van der Hoeve. He pointed out that it was also distinguished by abnormal bone fragility and, often, though not constantly, by defective hearing, which may sometimes amount to complete deafness.

To the morbid bone fragility Lobstein in 1829 gave the name *osteoporosis*. It may affect the entire bony structure or only sections and seems to be due not to true defective osteogenesis, but rather to the fibrils in the connective tissue of the bones being thinner and scarcer than in normal bones.

Ponzi describes and illustrates by X-ray photographs, pelvic deformities in 4 cases (3 sisters and a mother) due to osteoporosis.

The arrival of the 1st patient in his hospital took place near the end of her 2nd pregnancy. The presence of marked blue sclerotic along with pelvic defects induced him to make an examination of her family, since from clinical data collected from 5 generations in the local ophthalmic institute, Cordero had written a monograph on the heredity of the syndrome.

Ponzi found that in all 4 cases the effects of the syndrome were well marked in the pelvic bones. Radiographs showed abnormal transparency, rarefaction of trabeculae and flattening of the pelvis. In 2 cases asymmetry was more marked, because there had been fractures of one thigh in childhood. In all cases the true conjugate diameter was shortened.

He examined a 4th sister with normal sclerotics, and in her case the pelvic bones were normal in opacity.

He counsels accurate pelvic examination and measurement in obstetric visits, if a general examination has detected the characteristic sign of blue sclerotic.

FIRST OBSERVATIONS ON THE CLINICO-THERAPEUTIC VALUE OF A NEW OESTROGEN PREPARATION—DIETHYLDIOSSISTILBENE.

Lorenzetti reviews the chemico-biological history of preparations of oestrogen, a substance intimately connected with the phenol group, and which can be chemically deprived of oestrogeneous power. Folliculin, first obtained in pure crystals by Doisy and Butenandt, may be considered the prototype of oestrogens and has been standardized. Since its isolation it is found that the addition of certain substances such as benzoic acid increases the power of oestrogen. Recently chemical experiments have shown that the most active and durable synthesis is 4-4 dioxydiethlystilbene which is remarkably similar in structure to the two natural female hormones folliculin and oestradiol.

For a few months Lorenzetti has employed this preparation (Cyrene—Bayer) in the treatment of various ovarian and uterine diseases, and now publishes successful results in 21 cases. No serious inconvenience was experienced by any patient, but he never gave more than moderate doses and for limited periods of time. Under these conditions he recommends the drug because it is less expensive and more efficacious than some other oestrogens. Since some other authors have noted gastric and hepatic disturbances, further clinical trials are advised before definite conclusions are reached.

THE CONTROL OF BIOLOGICAL ACTIVITY OF THE FEMALE HORMONE.

After experiments for the control of oestrogens by various methods, the authors conclude that some methods owe results to the sensibility of the animals used, others to substances associated with the oestrone.

Brownlee found it useful for commercial purposes to estimate the value of the hormone by the increase in uterine weight of oöphorectomized rats, others by the increase in ovarian weight of immature rats.

The authors compare three methods: (1) by oestrum provoked in castrated rats, (2) by 100 per cent increase of uterine weight in immature rats and (3) by 400 per cent increase of ovarian weight in immature rats. For the injections they employed oestrone, oestradiol, and benzoate of purest oestradiol. The results varied and made it difficult to decide which substance was most active. Combining oestradiol with palmitic acid, ricinoleicic acid, or stearilic alcohol, it was found that each, particularly stearilic alcohol, increased and protracted the power of oestradiol. It also provoked an increase in uterine weight earlier, at the 4th day. Diminution in weight happened more slowly and after 15 days was greater than the maximal weight gained after injecting oestradiol alone.

J. H. FILSHILL.

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March, 1940.

Hysterosalpingography in sterility. F. Savignoni.

*Unusual injuries of the genital organs in coitus. F. Giuffrida.

*The undesirability of uterine curettage for diagnosis of extra-uterine pregnancy. E. Debiasi.

April, 1940.

*Significance of the gono-reaction in the normal and morbid puerperium. A. Tavella.

*Enlargement of the left breast and left lobe of the thyroid during four successive pregnancies. G. Amabile.

Unsuspected intramural pregnancy.

Ergobasin compared with a combination of ergotamine and ergobasin. F. Guercio.

May, 1940.

Experimental formation of fibromata by injection of follicular hormone. E. L. Custo.

Torsion of normal adnexa during the third month of pregnancy: acute abdominal symptoms: operation. R. Sassi.

Death two days after labour: bifid uterus, salpingitis and twisted ovarian cyst. E. Marchese.

Male sex-hormones in gynaecology. G. Lucchetti.

Should not veterinary science be applied to obstetrics and gynaecology? O. Viano.

Unusual Injuries of the Genital Organs in Coitus.

These injuries occurred in a robust girl aged 14 years as a consequence of a first completed coitus and two others following at a few hours' intervals. The bleeding after the 3rd attempt was sufficient to require improvised tamponnage by the partner. Examination showed a linear wound, 4 cm. long, and 4 cm. deep, in the right labium majus: it communicated in front by a small foramen with the vestibule.

Undesirability of Uterine Curettage for Diagnosis of Extra-uterine Pregnancy.

Curettage as an aid to diagnosis in suspected ectopic gestation was sponsored by Cohnstein in 1877 but has now fallen into disrepute. Its risks are obvious, and Debiaso records 2 cases which show that its utility is doubtful. In the first, laparotomy, after removal by blunt scraper of the endometrium had shown it to be "hyperplastic, in the early secretory phase," demonstrated recent right tubal abortion and right follicular ovarian cysts. The second patient expelled a typical triangular cast, microscopically of decidual character: operation, however, revealed no trace of present or

previous tubal pregnancy, but sclerocystic ovaries on both sides. Siddall (*Amer. Journ. Obstet. and Gynecol.*, 1936) found decidua in the endometrium in 38.6 per cent of cases of ectopic pregnancy in which it was examined, and in a percentage which diminished with the duration of the vaginal haemorrhage. The conditions in which the uterine mucosa may present decidual transformation in the absence of ectopic pregnancy are enumerated thus: (1) There may be menstrual decidua-formation. (2) Extremely early abortion of intra-uterine pregnancy. (3) Expulsion of decidua from the non-gravid half of a pregnant duplex uterus. (4) Following "mechanical insults". (5) The non-menstrual endometrial hypertrophy of Robert Meyer. (6) Persisting corpus luteum. (7) Membranous dysmenorrhoea.

THE GONO-REACTION IN THE NORMAL AND MORBID PUERPERIUM.

Tavella has convinced himself of the superiority of the haemolytic over the flocculation method in the complement-fixation test for gonorrhoea. Even in the absence of a history or of physical signs pointing to gonorrhoea he accepts the serological test as a reliable index of diagnosis and treatment. In puerperia respectively classified as afebrile, subfebrile, pathological and post-abortive he found the gono-reaction to be positive in 23.9, 26.5, 52.6 and 21.1 per cent. The totals of all the different groups are not large: 230, 49, 19, and 47 respectively.

ENLARGEMENT OF THE LEFT BREAST AND LEFT LOBE OF THE THYROID DURING FOUR SUCCESSIVE PREGNANCIES.

Amabile's patient was 34 years old during her last pregnancy: the left breast was about 8 times as large as the right and in the slightly enlarged thyroid the left lobe was the larger. Biopsy was impracticable. The response to endocrine medication was as follows, and is illustrated by photographs. Follicular hormone (progynon B oleosum) led to much enlargement; corpus luteum hormone (proluton Schering) to no change; thyroid hormone (Elitrynan Bayer) to slight decrease in size; and testosterone propionate (testoviron Schering) to well-marked repression of the swelling. Pilocarpine was ineffective.

W. E. CROWTHER.

REPORTS OF SOCIETIES

ROYAL ACADEMY OF MEDICINE, IRELAND.

A meeting of the Section of Obstetrics of the Royal Academy of Medicine in Ireland was held in the Royal College of Physicians on Friday, October 11th, 1940; the President, Dr. R. M. Corbet, was in the Chair.

The President, Dr. R. M. CORBET, read

NOTES OF AN UNUSUAL CASE OF ACCIDENTAL HAEMORRHAGE WHICH HAD TERMINATED FATALLY FROM URAEMIA.

The patient was aged 37 and at approximately the 30th week of her 2nd pregnancy. Up to a week before the onset, the urine was free of albumin.

The onset was sudden, commencing with severe pain in the abdomen, back and head. This was followed in about 6 hours by a light coma. When seen, the patient had the typical signs of toxic accidental haemorrhage, and was bleeding a little. She developed a complete anuria; Caesarean hysterectomy was performed approximately 36 hours after the onset of the attack. The anuria persisted for 36 hours more and was apparently relieved by the administration of isotonic sodium sulphate, which was given intravenously by the drip method.

At this time a lumbar puncture showed the cerebro-spinal fluid to be intimately mixed with blood. The patient's general condition improved for a few days. Her urinary output increased; but her blood-urea showed a steady and persistent rise. A week after the attack, she became sufficiently conscious to eat, and to ask and answer questions, but her cerebration was very slow. In spite of the increased urinary output, the blood-urea continued to rise. The coma returned and she died 17 days after the attack.

The kidneys, which were large and pale, showed considerable fibrosis and advanced degeneration; though the glomeruli were, for the most part, normal.

Dr. J. CUNNINGHAM said that this paper drew attention to the importance of giving a guarded prognosis in cases of accidental haemorrhage. In these cases, especially in the cases of concealed haemorrhage, Caesarean section should, in his opinion, not be done. But in very severe cases with anuria it should be done at once, and any risk which might be involved had to be taken. The most important thing was to watch the blood-urea. As long

as it continued to rise, the prognosis was bad. The principal thing in the condition of these patients was the toxaemia, and, even though they recovered from the haemorrhage, they might not live.

Dr. O'DONEL BROWN asked why a sub-total hysterectomy had been done in this case in preference to a classical Caesarean section?

Dr. G. C. DOCKERAY said that the section of the kidney which the President had shown, did not look to him like bilateral cortical necrosis. Judging by its appearance, he would say that the appearances were those of chronic fibrositis. He referred to a somewhat similar case which he had seen recently, in which the decapsulation of the kidney had been followed by the patient's death.

Dr. T. M. HEALY said that this case presented many features which were both unusual and interesting. The treatment which Dr. Corbet had carried out was one which offered the greatest temptation at the time. In such cases of accidental haemorrhage he thought that it made very little difference whether obstetrical or surgical treatment was adopted, as he believed that uterine haemorrhage was seldom fatal. Death, in his view, was caused by the toxaemia, of which the uterine haemorrhage was but one manifestation.

The Master of the Rotunda Hospital, Dr. A. H. DAVIDSON, said that this was an extremely interesting case with many unusual features. He had seen 2 or 3 cases which were somewhat similar up to a point, but differed in the way in which the urine acted. He believed that in most cases of toxaemia the condition was due to an ischaemia of the kidney owing to a narrowing of the blood-vessels; if the ischaemia was carried far enough the condition of bilateral cortical necrosis arose. Possibly this had occurred in the present case. In cases of accidental haemorrhage which did not respond at once to ordinary treatment, Caesarean section should be done as soon as possible. In his opinion it was not adopted often enough. In each of the cases he had seen, he was sorry he had not interfered sooner.

The President thanked the members of the Section for the kind way in which they had received his communication.

In answer to Professor O'Donel Browne, he said he did hysterectomy for the sake of speed in the operation and because it got rid of any possible uterine source of toxin. He agreed with Professor Davidson that he might have operated 12 hours earlier, and he was sorry he had not done so, but at that time the patient's general condition was so good, and as there had been a little urine on catheterization he did not feel justified in taking such a drastic step. He was sorry he had not divided the capsules of the kidneys at operation but he did palpate them and they did not feel under tension; neither did post-mortem examination show the cortical necrosis for which this treatment is said to be effective. At a later date he had discussed decapsulation with Mr. Lane, who advised against it.

He would like to stress the peculiarity of the coma. In the first instance, it was not uraemic coma, as the patient's blood-urea at this time was low, nor was it like the coma of eclampsia, as it maintained an even, shallow depth for days. It seems probable that it was attributable to the blood

found in the cerebro-spinal fluid. On the other hand, the terminal coma was certainly of uraemic origin.

He thought that the intravenous sodium sulphate had proved of value in promoting secretion of urine and that, had there been less damage to the tubules, the outcome might have been successful.

The haemorrhage itself had never been a big factor in the case, as the patient's blood never contained less than 50 per cent of red cells.

Dr. T. M. Healy reported

Six Hundred Rubin's Tests Under Ether Anaesthesia and Using Bonney's Apparatus.

There were no ill effects. He had then used carbon dioxide for the test in a smaller series of patients who were anaesthetized with nitrous oxide and oxygen. Three of these patients, who were physically normal, and whose tubes were patent, had died; 2 on the table, and one 30 hours afterwards with symptoms of damage to the cerebral cortex. He realized that much of the value of his communication was lost as he had not been allowed to carry out post-mortem examinations. He had found, in contrasting parallel series of cases, that the pressure of carbon dioxide averaged 10 mm. Hg higher than was required when air or oxygen was used.

He discussed the possible causes of death in the fatal cases, and said that while there were many minor surgical procedures, there was no such thing as a minor anaesthetic.

Dr. Bethel Solomons said a communication like this was opportune as he had heard and read of isolated fatalities after the Rubin test. It seemed nearly impossible to decide on the cause of death in Dr. Healy's patients; although the anaesthetics had been given by juniors the cause did not seem to him to be there. The presence of lipiodol in the sinuses after injection of that substance seemed to suggest that some form of embolism was a more likely cause. He did not believe that the type of instrument mattered; the man behind the instrument did: but it appeared as if carbon dioxide was a direct irritant and he intended to use oxygen in future. He believed that curettage had a very small place in the treatment of sterility.

Even if the greatest care were taken to exclude infection, rare cases of peritonitis were reported and he had had one in his practice.

It was quite possible to perform the Rubin test, watch the manometer and listen over the hypogastrium with a De Lee's stethoscope.

Dr. F. W. Doyle said that he recently had under his care a somewhat similar case. The patient had sterility of about six months' standing, associated with dyspareunia. The patient was given a spinal anaesthetic, preceded by morphia and hyoscine: the Fallopian tubes were found to be absolutely blocked. The uterus was then curetted. The patient was quite conscious, and suddenly said that she was in great pain. She then became cyanosed, collapsed, and died in a short time. A post-mortem examination was not permitted. He had used a cylinder of oxygen, and

the pressure had gone up as far as 200 mm. Hg. He wondered was it wise to use a cylinder, or should an ordinary pump be used.

Dr. J. F. CUNNINGHAM described the technique he employed in doing Rubin's test, and said that he always preferred to do it without an anaesthetic. In his opinion the most important thing in doing the test was the technique. Great care should be taken not to injure the cervix. He always used a very fine catheter which only went into the uterus for about an inch and three-quarters. If bleeding occurred, he stopped the test at once. He did not think that the person who was carrying out the test could listen carefully with a stethoscope and watch the manometer at the same time.

Dr. O'DONEL BROWNE said that he knew Dr. Healy had the sympathy of the Section for 3 unfortunate deaths following Rubin's test. He quoted from several hundred cases of tests among which there had been 1 fatality —that already referred to by Dr. Bethel Solomons.

This particular patient had died in the Rotunda Hospital following Rubin's test which he had done for Dr. Solomons one Friday morning; death occurred the following Sunday afternoon from streptococcal peritonitis.

Dr. O'Donel Browne stated, that in his opinion, Rubin's test could be done in an out-patient department, either for hospital or private patients; an anaesthetic was not required and premedication, or internal trauma, was not necessary. He did not use a bullet-forceps on the cervix, passed as little gas as possible through the Fallopian tubes, never hesitated to allow the pressure to rise to at least 250 mm. of mercury, and was most satisfied with the results.

He thought it very wrong indeed that any blame should be attached in Dr. Healy's cases to the form of anaesthetic used, but preferred to eliminate this possible risk in his own work and in consequence did the tests without any anaesthetic.

Dr. G. C. DOCKERAY said that 4 years ago he had had occasion to look up in the literature the subject of air embolism, and he had found that the two chief causes of it were Rubin's test and artificial pneumothorax.

Dr. E. SHAW said that it was impossible to arrive at a definite conclusion as to what had been the cause of death in Dr. Healy's cases because post-mortem examinations had not been permitted. In cases in which Rubin's test was carried out, very often the blocked tubes were very widely dilated and so was the uterus. This, he thought, caused shock, and such shock might easily be the cause of death. Of one thing he was quite certain and that was that no patient should ever die from a properly given anaesthetic. In his opinion any kind of premedication with a spinal anaesthetic was a definite risk. If he ever had to use any kind of premedication he gave a few grains of nembutal by the mouth. An anaesthetic death occurring on the operating table should not be attributed to the anaesthetic, but to the anaesthetist.

Dr. EDWARD SOLOMONS said that vaginal insufflation by air produced air embolism as well as Rubin's test. He referred to a case which had been

reported by Pierce in which vaginal insufflation had been done and although an anaesthetic was not used, the patient had died. This patient was 4 months pregnant. He asked if any abnormality had been found on pelvic examination in any of Dr. Healy's cases.

The Master of the Rotunda Hospital, Dr. A. H. DAVIDSON, described his technique for carrying out Rubin's test, and said that it was exactly the same as that of Dr. Bethel Solomons. In the last 15 years he had done about 1,000 cases. When treating city patients it was possible to arrange for them to come and have the test done in the intermenstrual interval. In hospital cases however it was often necessary to do it at a time which was not the most suitable in relation to the period. When the test was done the Fallopian tubes often appeared to be blocked. He usually curetted the uterus and then did the test again. He had done this in about 400 cases, and had found that in 60 per cent of these the tubes which had appeared to be blocked before curettage were not blocked after it had been done. He had never seen a case in which there had been any sign of air embolism, and found it very hard to believe that air embolism following Rubin's test was really a fact. After curettage he put lipiodol into the Fallopian tubes, and he had only seen one case in which this had produced any ill effect. He always allowed the pressure to rise to 250 mm. Hg. In his opinion Rubin's test was not of any great value if it was merely regarded as an aid to show that the Fallopian tubes were patent before curettage. The anaesthetic he always used was gas and oxygen.

Dr. VICTOR MCCORMICK said that he found it almost impossible to believe that any fatalities with Rubin's test could be written off as anaesthetic deaths. Any patient who had arterio-sclerosis was, of course, not a suitable subject for gas and oxygen anaesthesia. Air embolism seemed to be too rare a condition to be accepted as a real entity. Paralysis of the external rectus oculi muscle sometimes occurred as a late sequel of spinal anaesthesia, and was quite inexplicable. He wondered if any mechanism, similar to trauma, could be operative when the Fallopian tubes and uterus were subjected to dilatation by gas. Was it possible that some reflex action could have been operative in Dr. Healy's cases and have given rise to death, such as sometimes occurred in cases of criminal abortion?

Dr. E. A. KEELAN said that his only concern in carrying out Rubin's test up to the present time had been to ensure that the cannula had not a too freely movable cork. He had on one occasion found the cork too near the tip of the cannula and had thought that he would move it. This he had found it hard to do, and he had used a sterile lubricant, and then the cork had moved so freely that he realized the possibility of perforating the uterus with the cannula, if much pressure was used in keeping the cork in position against the external os uteri.

The President said that, before calling on Dr. Healy to reply, he would like to thank him for the extremely interesting and valuable communication which had given rise to such discussion.

It was difficult to assess what points in the technique of this operation really mattered when one heard the descriptions given by the Masters of

the Rotunda Hospital and of the National Maternity Hospital of methods which one might almost describe as being directly opposed to one another.

The President used a technique rather like that described by the Master of the Rotunda Hospital. The cervix was dilated to admit a No. 8 Hegar's dilator which was the size of the Bonney's cannula used. Carbon dioxide was used as the inflating gas with a manometer attached to the side of a metal box, such as was described by Dr. Solomons. If the gas did not pass through the Fallopian tubes with a pressure of not more than 200 millimetres of mercury the uterus was curetted and the test tried again. The patient, during the operation, was under full ether anaesthesia.

From the evidence presented by Dr. Healy and the subsequent discussion, it appeared difficult to dissociate the fatalities from the use of carbon dioxide as an insufflating gas while the patient was being anaesthetized with nitrous oxide and oxygen. It seems probable that, of the 5 cases mentioned, air embolism could not have accounted for those which survived for some time after the initial collapse and, in 2 of the remaining 3 cases, there is the possibility of shock occurring with imperfect anaesthesia.

He considered that Dr. Healy had done a very great service in bringing to our notice, in this dramatic way, the dangers of this apparently trivial operation.

Dr. Healy, in reply, said that he had abandoned curettage in cases in which Rubin's test was negative because of the risk of embolism. Now, however, he thought he would start doing it again. In his 3rd case it was very difficult to explain how an air embolism could have been the cause of death. He questioned very much whether the procedure of Rubin's test was worth all the trouble it entailed. In all his cases the Fallopian tubes had been patent. He did not think that in any of his cases more than 100 c.c. of carbon dioxide had passed into the uterus and Fallopian tubes, and it was rather hard to think that this could have been the cause of shock sufficient to give rise to death. The best time to do the test was within 10 days of the end of the menstrual period. He would like to make a plea for more and better anaesthetists. The same amount of skill, knowledge and care should be required from an anaesthetist as from a surgeon. Referring to the possibility of perforating the uterus during a Rubin's test, or prior to it, he said that he had once done this with dilators immediately prior to doing the test. He thought that carbon dioxide was an irritant to the Fallopian tubes.

A Meeting of the Section of Obstetrics of the Royal Academy of Medicine in Ireland was held in the Royal College of Physicians on Friday, January 24th, 1941; the President, Dr. R. M. Corbet, was in the Chair.

Dr. BETHEL SOLOMONS showed

AN UNUSUAL TUMOUR OF THE VULVA.

The patient was aged 29 and was born in the Rotunda Hospital in March 1911. At birth there was an abnormality of the vagina, rectum and bladder of congenital origin.

Eighteen months after birth Dr. Jellett operated. He made an incision backwards to the perineum from the abnormal anus to the site of the normal one. The sphincter was divided, and the edges of the mucous membrane of the rectum were tied with interrupted catgut sutures to the skin. A large mass of faecal matter was removed with a blunt instrument, and finally an enema of olive oil was given. She was discharged apparently cured on October 9th, 1912.

She was seen by Dr. Bethel Solomons in September 1940, when she complained of a mass in the vulva, which she had never worried much about, but now she wished to marry. On examination a mass was apparent; it was an elastic yielding compressible swelling about the size of a Victoria plum; it was eroded and there were two crypts which did not admit a ureteral catheter. The mass was anterior to the anterior vaginal wall. The urethral orifice was to the left side of the mass. The vaginal orifice admitted a finger, but the rectal orifice was very distended and appeared to be inflamed. There was no perineal body, and the vaginal and rectal orifices were separated only by a thin stratum. All her functions, including menstruation, were normal.

Dr. SOLOMONS performed the following operation, which had to be done with great care because of the danger to the bladder and ureter. A circular incision was made around the protruding mass and a line of cleavage was found. A catheter was kept in the urethra and the bladder was found to be just above the mass. A thin cord was found running down the right side of the growth and was suspected of being the end of the right round ligament. The main mass was of loose connective tissue and was excised. Some deep catgut sutures were inserted to close the cavity and the edges of the wound were closed with continuous catgut sutures and a few interrupted stitches of silkworm gut. A small drainage tube was inserted in the cavity.

Pathologically the main part of the mass seemed to be typical intestinal epithelium, with mucous glands and some inflammatory cells; and below muscle fibres arranged in bundles suggested intestinal wall. Part of the tumour is covered by squamous epithelium. The mass is a congenital abnormality of unknown origin and did not follow any known pattern of embryological error.

Convalescence was almost without incident.

The President thanked Dr. Solomons for the extremely interesting and rare specimen which he had brought to the notice of the Society.

The histological report suggested that the mass was composed of ectopic intestinal tissue; he congratulated Dr. Solomons and the Rotunda Hospital on being able to produce such complete notes on the conditions found in this patient 30 years ago.

THE MASTER of the National Maternity Hospital said that this was a most interesting specimen and Dr. Solomons was to be congratulated on the splendid result he had achieved. This tumour was apparently due to a congenital abnormality, as a result of some displaced intestinal tissue which had produced the abnormality. He asked if everything else in the vagina was quite normal. It would be interesting to see if there was any abnormality in the pelvis, because if the patient became pregnant, her pelvis was likely to be damaged.

Dr. J. S. QUIN said that it would be of great interest to know how much this condition was congenital and how much it might have been due to some post-operative condition. The difficulties of operating in a child only one year old, with a very doubtful condition, must have been considerable.

Dr. Bethel Solomons replied.

Dr. OLIVER CHANCE read

NOTES ON THE RADIATION TREATMENT OF CANCER OF THE CERVIX.

The speaker apologized for bringing up the hackneyed subject of carcinoma of the cervix. He came to provide material for discussion and to learn from the greater experience of others.

The paper was based on 201 cases examined between 1930 and 1937. These were classified according to the League of Nations recommendations and most of them came from gynaecologists. The cases were studied from the point of view of age, duration of symptoms and marital history.

The method of radiological treatment at present used by the speaker was described and figures were shown which illustrated the great value of combined X-ray therapy with radium therapy, particularly in advanced cases. The results, 5 years after treatment had been given, were shown in tables in which the nett, gross and absolute survival figures were shown for each group, and for the cases as a whole.

THE PRESIDENT said that Dr. Chance need not have had any diffidence in talking to gynaecologists about carcinoma of the cervix. He was sure few, if any, Dublin gynaecologists could produce over 300 cases.

He was glad that Dr. Chance had referred to the importance of inspecting the cervix in gynaecological examinations. This should always be done. He felt that this examination was too often omitted in patients who came to have pessaries changed. As these patients were frequently in the common age-group for carcinoma, the omission here was particularly dangerous.

He would also stress routine examination of curettings, in cases of prolapse, and of cervices removed in the treatment of prolapse by the Manchester operation. On four occasions, he had found completely unsuspected carcinoma, two of the body, and two of the cervix.

He felt he was not justified in performing the Wertheim's operation owing to the high primary mortality. In this, he followed the view expressed by Crossen, the well-known American gynaecologist.

He congratulated Dr. Chance on the results he had produced, considering the somewhat adverse conditions under which he was forced to work.

Dr. GIBBON FITZGIBBON asked Mr. Chance if he could give any figures to indicate whether gynaecologists were doing much harm or any good in operating on operable cases and then sending the patients to him for radium treatment. Should these cases be left entirely to radium treatment, or had operative therapy still got a place?

Dr. BETHEL SOLOMONS said he did not agree that gynaecologists in Ireland were sick of cancer of the cervix—they saw too little of it. He accounted for this by the absence of meddlesome midwifery, the careful examination which was made of the cervix at gynaecological clinics, and the tracheleorrhapies which were performed. As there is so little cancer of the cervix in Ireland, he advised against the Wertheim operation which, he said, should be done only by surgeons who had constant practice. If a cancer institute were established then the question of the radical operation could be considered.

He asked if among the 12 per cent of the cases of cancer in nulliparae there were any women who had had operations on the cervix. He had reported one case of epithelioma of the cervix following posterior division. Was great care taken to ascertain if any of the probable nulliparae had had any abortions? Had Mr. Chance inserted radium inside the abdomen?

He thought that the figures presented were extremely satisfactory, when one considered the small number of cases and the difficulty under which Mr. Chance worked.

The MASTER of the National Maternity Hospital said that Mr. Chance need not be diffident about the results he had obtained in comparison with other hospitals, when he took into account the tremendous difficulties under which he had to work. He had to work with radon instead of with radium element. It was, in his opinion, rather a scandalous thing that no effort at all had been made to try to obtain radium element for Dublin. He did not agree with those people who said that a good Wertheim's hysterectomy could not be done in Dublin. In his opinion any gynaecologist who was accustomed to doing abdominal work could well do Wertheim's hysterectomy. He was not quite convinced that this operation was wrong in the treatment of carcinoma of the cervix, but it was very important to pick with great care the cases in which it was done. It should never be done in third- and fourth-stage cases, but in the earlier cases he thought there was a place for it.

Dr. D. RIORDAN referred to the difficulties of obtaining radium element in Dublin, and said that he had worked for some time in a hospital in Manchester where there was every possible facility for treatment. He had been specially interested in cases of cancer of the cervix, and particularly in the unfortunate reactions which sometimes followed radium treatment, such as ulceration of the rectum. This was due to misplacement of the radium in the vagina. In the operating theatre in the hospital in Manchester where he had worked there was a special table to which, as soon as the radium had been given, the patients could be transferred and X-rayed. This made certain that the radium remained in position. The uterus apparently tended to fall backwards as soon as the radium tube was put into it. Another complication was induration of the rectal wall with ulceration, and another rather common one was the formation of a fistula. This was caused by treating advanced cases while there was actual involvement of the rectum. Radium should not be given in cases in which there was a stricture.

Dr. J. G. GALLAGHER said that he was interested to hear Mr. Chance in his paper state that carcinoma of the cervix seemed to be infrequent in Ireland. In New York, when he had been there recently, a list which he had seen had shown that Irish people ranked either second or third amongst patients with this disease.

Dr. J. S. QUIN said that it would appear that surgery as a treatment for carcinoma of the cervix was dying out in Ireland. He had yet to see a patient who had been operated on for carcinoma of the cervix in Dublin who was alive 5 years after the operation had been performed. The question of the frequency of carcinoma of the cervix in Ireland was a matter which deserved further study. In the Rotunda Hospital an average of only 10 to 15 cases of carcinoma of the cervix was seen per annum. Of these cases, it was unlikely that more than 9 of them would be suitable for operation. Nobody doing only 9 cases of Wertheim's hysterectomy a year could be described as anything more than an occasional operator. The splendid results which Mr. Chance had obtained had been achieved in circumstances of the most extreme difficulty. These difficulties had not been at all sufficiently stressed by him in his paper. He had no control over his main therapeutic agent, radon. He had had two cases of erosion treated by Mr. Chance with a sort of half cancer dose, and it had been found that there was no radon in the tubes; the patients had naturally had no reaction whatever after the treatment.

Dr. EDWARD SOLOMONS asked Mr. Chance if he ever carried out X-ray treatment before he inserted the radium. He understood that in many places this was done as a routine. In Germany every patient had her pituitary gland treated by X-rays before she was given radium. Was this any use, and should it be done as a routine measure?

The MASTER of the Rotunda Hospital said that a personal friend of his had had Wertheim's hysterectomy performed in Dublin and had lived for 9 years after the operation. He could think of many other patients who had lived for 9 or 10 years.

Mr. CHANCE in reply said that he thought that Wertheim's hysterectomy might now be considered dead. If enough figures were taken into consideration it was possible to come to a definite conclusion, but it was impossible to compare one clinic with another. One patient in his series had been a chronic pessary wearer. Referring to radium treatment after surgery he said that it had to be remembered that one was dealing with very big doses of radium, and that if radium got to the wrong place it would do a considerable amount of harm. It was a very difficult job for the radio-therapist to treat a post-operative case effectively. He had counted abortions in the number of his cases who had become pregnant after treatment. Radium put into the abdomen was not as effective as adequate X-ray treatment combined with radium.